11

Prediction of Feeding Behaviour from Energy Flows in the Rat

D. A. BOOTH
Department of Psychology, University of Birmingham, England

The components of our model of hunger processes in the rat (Mark 3 version) and some of the results of simulation have been stated in reviews elsewhere (Booth *et al.*, 1976; Booth, 1976). This chapter records how the model developed. That is a way of describing the model itself which may help it be comprehensible to someone who happens to be unfamiliar with either computer simulation or our theoretical orientation, or perhaps both. Indeed, an unfamiliar systems analysis of any complexity is daunting to almost anyone in its final form, and a good route to the "inside" of any system is to follow its elaboration from some simple precursor along a series of "natural" modifications. Such an account also illustrates our views as to the relationships one should endeavour to maintain between modelling, theorizing, use of the experimental literature, and the design of new experiments.

I. Background Concepts and Theory

A. *The Physiological Control Systems Approach*

Oatley (1967) presented an account of the physiological basis of mammalian thirst using the concepts of control engineering. These had been used previously in physiological analysis but Oatley extended the analysis of a system of physiological components to include what any psychologist would categorize as motivational behaviour. The components of his model represented the current understanding of the physiology and psychology of those aspects of the real

animal which control its water intake and the disposal of water throughout its body. Toates and Oatley (1969) presented a digital computer simulation for the rat of a quantitative version of Oatley's analysis and put it to use to examine the plausibility of certain differing theoretical accounts of rats' drinking responses. The quantitative predictions of water intake were tolerably realistic, with some instructive differences between modelled behaviour and results from real rats. Later developments of this approach to computed theory of drinking control are discussed by Oatley (1973, 1974) and Toates (1974, 1975).

Between 1967 and 1972, Oatley and I discussed several ways in which a computer simulation of feeding and its physiological basis might be constructed for the rat. We never quite convinced each other that we yet had an adequately realistic and fully workable analysis of the system. However, in early 1973 Toates became keen to work on the construction of an "eating computer". We were not aware of any other computer simulation of food intake, although when I presented our model at Ermenonville later in the year, Panksepp called my attention to Hirsch (1972)—reprinted as Chapter 4 in this book. His model was in a more abstract style, without directly and independently measurable component functions. Also it worked on daily jumps, not on meal-to-meal real time processing. At a still later stage, at the Jerusalem conference in 1974, Barnwell presented neural network equations he had constructed a couple of years previously (see Chapter 5), and—most relevant of all—Schilstra drew my attention to Geertsema's (1973) PhD Thesis, a summary of which had just become available in English (Geertsema and Reddingius, 1974); Geertsema's modelling work is reviewed here in Chapter 9. These models were also more conceptual than the attempt Toates and I envisaged. We wanted to use simple but measurably realistic models of actual components of the body and behaviour, interconnected in the simulation in the way they are in the real rat, and see if we could predict feeding behaviour which was quantitatively realistic—for example, meal sizes and intervals between them of the right size and typically distributed around the clock.

B. *The Energy Supply Theory of Satiety/Appetite*

The enterprise might be viable only if we had sufficiently realistic characterizations of the main components of the system, if these were programmable, and of course if the theory informing the selection of relevant components and their interconnections was somewhere near the truth.

I had become convinced in the previous couple of years that at one level of analysis the theory of hunger physiology could be considerably simplified. I had suggested that there was a set of satiety signals or a single signal which reflected the current supply of readily metabolized energy (Booth, 1972a, b, d). The initial evidence for this view was the finding that a wide variety of energy-

yielding nutrients or metabolites had a suppressant effect on food intake following their absorption, and their satiating effect was related to their energy yield independently of their convertability to glucose (Booth, 1972d). Additional considerations (see pp. 270–271) encouraged the extension of this idea to the hypothesis that feeding in the rat was under the control of a single main factor—an "energostatic" or energy supply stabilizing system (Booth, 1972a, d), better termed "ischymetric" or power measuring (Nicolaïdis 1974).

To assert that a more or less unitary complex of stimuli from energy metabolism directly or indirectly exerts the most important single influence on feeding is not to deny that feeding can be affected by a change in one or more of a multitude of variables. From a single-factor viewpoint, these variations are either extraneous constraints within which the basic energy control system has to work or variations which are correlatable with events in the energy control system and so can be incorporated into it by learning mechanisms.

Once the notion that energy supply ruled appetite had been formulated, glimmerings of how to calculate energy supply began to take form and the range of experimental design that seemed likely to be usefully relevant narrowed sharply.

1. *Direct and Indirect Control*

The supply of energy to the relevant tissues would be in direct control of feeding if there was an invariant consequence for onset, offset or selectivity of food intake when energy supply was in a particular state. Most experiments on the relation of physiology or biochemistry to behaviour in appetite are built on the assumption of direct control. The results can be meaningless if control is indirect (e.g. amino acid aversion: Booth and Simson, 1974; conditioned satiety and appetite: Booth, 1977).

The influence of energy metabolism may be indirect in two ways. Firstly, learning to predict energy effects of imposed, or organism-controlled situations, provides anticipatory control. Anticipatory actions can greatly influence the performance of the system, but then current energy supply is no longer the only influence of energy metabolism on feeding. Experience of states of energy metabolism which consistently follow both the organism's current state of metabolism and other aspects of its current state (external and internal) is important in interpreting the current metabolic state.

Secondly, at least some of the information which reflects energy metabolism may be provided to the nervous system not by metabolism itself, but by hormones or tissue innervation signalling events which are normally tightly connected with metabolism.

2. *Unitary but Fractionable Control*

The influence of energy metabolism may not from all points of view be strictly

unitary. At one level of analysis and to a certain degree of approximation, the flow of energy to a functional satiety/hunger transducer system may account for observed feeding behaviour and changes in body content under many conditions. At a more detailed or lower level of analysis, or under some unusual conditions, the transducer system will be seen to have component parts. Different aspects of energy metabolism may be sensed in different ways and by effects which are not exactly proportional to energy.

Metabolic control of feeding is unlikely to be restricted to energy metabolism, although I believe that hunger is normally dominated by current energy. Amino acid supply and the balance in the pattern of amino acids available to tissues can affect feeding independently of energy (Booth, 1974) again possibly largely via learning (Booth and Simson, 1974). Vitamin deficiencies, which disrupt metabolism, can also have marked effects on food intake (Harris *et al.*, 1933). However, the rat's feeding behaviour will not often be subject to such influences– in the laboratory because a single complete diet is provided and energy control brings all other necessary nutrients with it, and in the wild because many mixtures of foodstuffs consumed on an energy control basis provide sufficient vitamins and minerals, and often adequate protein too. A theory that considers only energy metabolism may therefore suffice for a wide range of circumstances. The model in this chapter is built on this basis. The information we have on behavioural and physiological effects of protein, vitamins and salts may be sufficient to elaborate the model to cover situations in which they become important independent variables, but we have only just begun to work on that.

Evidence for energy flow theory, its current paradigmatic advantages, and the relations between energy and other influences on hunger and satiety are reviewed elsewhere (Booth, 1978).

II. An Elemental Control Loop

Feeding affects energy flow. Energy flow, according to the theory, affects feeding. This implies that there exists a recurrent loop between the body and feeding behaviour. We might be able to calculate the loop's performance. Furthermore, feeding increases energy flow, whereas, on the energy supply theory of satiety and hunger, energy flow should inhibit feeding. Thus the loop has negative feedback characteristics. That is, there might on calculation of a model of the loop prove to be an elemental system capable of controlled or relatively stable performance. Not any negative feedback loop would do. The characteristics of the components would have to prove suitable. The system might oscillate continuously between feeding and not feeding, without staying in one or other state for any appreciable time. Even if the system modelled meals, it might very rapidly reach a cumulative state of energy content which would correspond to death by starvation or by explosion!

Toates and I therefore started designing a computer programme for the most elemental model, consisting of three components:

(i) a simulation of the process we believed to be most influential in the short term effects of feeding on energy flows within the rat;

(ii) a simulation of the effect of energy flow on the tendency to feed or not;

(iii) a simulation of the process of food intake itself.

A. *A Gut Clearance Function*

From what is known of rat physiology, we thought that the largest variation in energy flow to the tissues—and often the largest single category of energy flow in the body—was intestinal absorption. So the first aspect of energy processing we chose to simulate was gastrointestinal transit of food. During a year's collaboration in 1971, Davis had taught me to attend to the details of what normally happened to food between the mouth and the blood and to be sensitive to the inadequacy of the measurements and manipulations of gastric and intestinal processing then current in physiological psychology (Davis and Booth, 1974).

The rate of absorption is not limited by the rate of transport of digested nutrients across the intestinal wall, nor in normal circumstances by the rate of digestion. Absorption rate is usually determined by the rate at which chyme is pumped from the stomach into the duodenum. Thus, at least under steady state conditions, the way the stomach empties will largely determine the flow of energy to the tissues.

1. *Gastric Emptying Data*

At the time Toates and I started to build the elemental model, I had some data on gastrointestinal transit of glucose loads which approximated in energy the size of the rat's normal meals (Booth, 1972a, fig. 8), and Jarman had more detailed observations (Booth, 1971) since published (Booth and Jarman, 1976: fig. 3). From Hunt's theory of control of gastric emptying by an osmoreceptor in the duodenal wall (Hunt and Knox, 1968), I was disposed to believe that glucose loads and the starch and protein from a meal would pass from the stomach according to very similar functions, except perhaps for some initial transients. Laboratory chow for the rat is typically about half starch and one-fifth to one-quarter protein by weight, with only a few per cent of fats of all sorts. Later preliminary data on chow clearance did not discourage this view (Booth *et al.*, 1976: fig. 2). Furthermore, Hunt and Stubbs (1975) later adduced a variety of data consistent with the notion that—at least with fluid diets in man—gastric emptying was controlled according to the energy content of the stomach as it affects the duodenal wall osmoreceptors and fatty acid receptors, independently of the relative composition in carbohydrate, protein and fat. They also showed that gastric emptying rate was a function of the energy density of the meal. Our

glucose clearance data were mainly with 40% glucose (1·5 kcal/ml), which is similar in energy density to a mixture of chow and water taken in the proportion of about 1 g to 1 ml which is usual for an *ad libitum* meal (i.e. 1·6–1·7 kcal/ml), a coincidence which was lucky for the fate of the early version of the model.

The characteristics of the initial stages of gastric emptying were ill-defined and remain so, at least for intubated fluid loads in both rat and man. Hunt and Knox (1968) drew attention to the variations in the extrapolated intercept on the gastric contents co-ordinate when an exponential function was fitted to plots of gastric contents against time for about the first hour in different human subjects. The extrapolated "starting times" for the load given, and the appearance in some circumstances of a phase of very rapid emptying compensated by a limited period of very slow emptying, represent deviations from an exponential emptying function in the first minutes following a load. Toates and I spent some time trying to settle on a calculation of initial transients, because they appeared likely to have a considerable effect on absorption rate towards the end of a meal, and hence on meal size. In the end we despaired of coping with the general ignorance of the details of earlier emptying and gave up that at this stage—perhaps fortunately, because these transients may be negligible or even absent with voluntarily ingested solid nutrients (Booth *et al.*, 1976: fig. 2; see Fig. 1 of this chapter), unless the animal takes a large meal or has been starved (Oatley and Toates, 1969; Wiepkiema *et al.*, 1972). In these circumstances an initial rush of food into the duodenum may occur before digestion can become sufficiently adapted to the meal to provide an appropriate strength of stimulus to the duodenal wall receptors inhibiting gastric emptying. When the digestive products of this undercontrolled rush are seen, they are abundant enough to stop gastric emptying almost completely until the excess has been absorbed.

2. *Gastrointestinal Processing of Chow* ad libitum

Newman and Nolan are currently collecting systematic data in my laboratory on gastric and intestinal contents in the rat following voluntary ingestion of a normal sized meal under close to *ad libitum* feeding and drinking conditions. The results put those earlier interpretations onto a much firmer basis. Stomach contents decline in a smooth curve, and the contents of intestinal segments vary little if at all under these conditions (Fig. 1). The rate of stomach emptying decreases with amount in the stomach, giving a much better fit by a quadratic equation than a linear equation, and no significant improvement on adding cubic or higher polynomial components. The quadratic function in time has an almost exact root—that is, the square root of amount in the stomach gives a stright line when plotted against time. When the curve is fitted to a power function, the exponent of time is almost exactly two, i.e. again, square root of stomach contents is linear against time. Finally, linear regression accounts for more of the variance and gives a much more realistic extrapolation to stomach contents at

zero time when carried out on the square root of stomach contents against time than on the logarithm of contents against time—i.e. the emptying function is not truly exponential when its whole time course is considered.

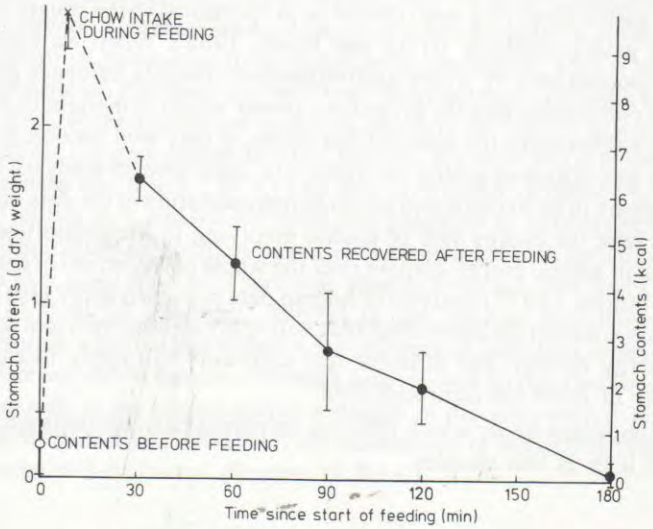

Fig. 1. Contents of stomachs at intervals following the ingestion of 3 g of chow by 325-g male rats in the middle of the dark phase of the lighting cycle. Solid circles represent amount recovered from the fed rats, and the cross their chow intake. The open circle is the amount recovered from rats identically pretreated but killed instead of being given food. A 240-min point was deleted for curve fitting calculations. The best quadratic fit ($F=97{\cdot}6$) was $A=9{\cdot}5-0{\cdot}075t+0{\cdot}00014t^2$ (where A is amount in the stomach in kcal and t is time in minutes). The linear, exponential and square root regression best fits were respectively $A=7{\cdot}89-0{\cdot}046t$, $\log A=1{\cdot}69-0{\cdot}0158t$, and $A^{\frac{1}{2}}=3{\cdot}24-0{\cdot}0165t$, with F-ratios of 101, 42·8 and 154·2. If the square root function is taken to represent this curve, then emptying rate as a function of amount in the stomach is simply derived as follows. Take $A^{\frac{1}{2}}=c-mt$. Squaring, $A=c^2-2mct+m^2t^2$. Differentiating, $dA/dt=-2mc+2m^2t=-2m(c-mt)=-2mA^{\frac{1}{2}}$. Thus, under the conditions of the data in this Figure, the energy rate of gastric clearance is the square root of the energy in the stomach multiplied by $(-2)(-0{\cdot}0165)=0{\cdot}033$ in kcal units. Data of Dr J. C. Newman with the assistance of Mrs Veronica Nolan.

If we measure the slope of the curve of gastric contents against time at any particular level of energy content, this gives the rate of gastric emptying for that stomach content. The simple mathematical statement of the same point is that the rate of change of amount in the stomach (dA/dt) is the first differential of the function which relates amount in the stomach (A) to time (t). Conveniently or confusingly, the first differential of a square root function is also a square root function (see caption to Fig. 1). That is, the rate of gastric emptying at any moment is proportional to the square root of the amount in the stomach. The proportionality factor (or rate constant) is minus two times the slope of the

straight line to which the curve of Fig. 1 is converted by plotting the square root of gastric energy contents against time. There is a tradition, from both Marbaix and Cannon at the turn of the century to Hopkins recently, that in so far as the stomach approximates to an elastic cylinder, its wall tension (which might well determine gastric emptying rate) should be proportional to the square root of the volume of gastric contents (Hunt and Knox, 1968). When we known more about the mechanisms by which gastrointestinal contents influence gastric and duodenal contractions and the propulsive power which is thought to arise from the pressure differences the contractions create, it may well become possible to reduce the description of gastric clearance to a lower level of analysis. Until that time, it appears to be a robust and accurate representation of the data on chow *ad libitum* to take the energy rate of gastric emptying to the proportional to the square root of gastric energy content over the whole of the period of emptying. If Hunt and Stubbs' (1975) analysis of human data proves to apply also to the rat, then the rate constant for chow clearance will apply to other nutrient mixtures of similar energy density, but different rate constants will apply to calorifically more dilute or more concentrated diets.

Other conditions under which different emptying rate constants apply will be mentioned later in this chapter.

3. *Calculation of Absorption Rate from the Gastric Clearance Function*

The stomach is emptying while it is being filled during a meal, as well as after the end of the meal. The calculation of emptying can be updated sufficiently frequently on the computer to mimic the continuity of the real process. Emptying is simply negative filling. Emptying and filling cumulate to yield the amount in the stomach which in turn determines emptying. This calculation of model stomach contents is represented diagrammatically in Fig. 2.

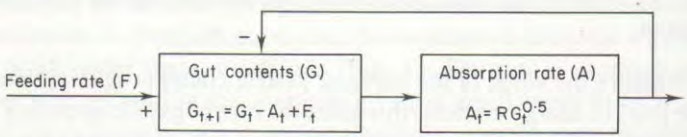

Fig. 2. Flow diagram for simplified gut clearance model. This can be simply represented in a series of calculations reiterated for intervals of real time sufficiently short to mimic the results of continuous differential equations. Thus, calculate the amount absorbed since the last calculation using the rate of absorption corresponding to the amount in the gut; from the rate of ingestion calculate the amount ingested since the last calculation; alter the amount in the gut by subtracting the absorption and adding any ingestion. Under the night time conditions of Fig. 1, the proportionality factor $k = 0{\cdot}033 \times \sqrt{1000} = 1{\cdot}04$ in small calorie units. In our first simulations, the night factor was 0·9 and the day factor 0·6.

We considered representing gastrointestinal processing as two compartments, stomach and intestine. However, the amount of computation and the number of variables on which there were few or no data seemed very large compared with the loss of accuracy involved in regarding the intestine contents as negligibly small in energy and in energy flow variance compared with the stomach contents. Therefore we used the square root function to cover the whole of gastrointestinal processing from ingestion to absorption. This is to make the implicit assumption that there is a very brief delay between ingesting a morsel of food and the absorbed digestion products reaching the tissues in which energy flow acts on the nervous system to affect feeding. We were aware at the time that Pilcher, Jarman and Booth (1974) had data on transfer of carbon to the brain and other tissues at 5 and 10 min after oral ingestion of radioactively labelled starch, extrapolation of which to zero transfer coincided with zero time within a resolution of a minute or so. There was already evidence that part (Rupe and Mayer, 1967) or all (Steffens, 1969b) of the glucose contributing to the hyperglycaemia which arises within a few minutes of ingestion arises from free glucose incorporated in the diet. Pilcher's data showed further that food can pass from the mouth to the tissues within a couple of minutes, even if digestion is required as it normally is. However, the inadequacy of neglecting even a 2-min delay is to be tackled below (Section IV.B.l.a.).

B. *A Hunger and Satiety Thresholds Function*

1. *The Two-Threshold Concept*

The basic idea of any energy supply theory of hunger/satiety would be expressed in its most primitive form by the statement that the propensity to feed appears when the flow of energy from absorption becomes too small and disappears again when absorptive flow becomes adequate or too great. As will be seen from later development of the model, I do not believe that either the flow from absorption alone or any uninterpreted energy flow is the determining factor. Nevertheless, additional energy flows could be incorporated later, as well as interactions with external conditions such as sensory qualities of the food and the time of day. The first step was to make a calculation on direct sensitivity to the major flow, absorption.

The simplest representation of this energy flow theory would be the rule that feeding started when absorption fell below a certain rate and stopped again when absorption rose above a certain rate. The step-function characteristic of the energy thresholds for the start and end of the meal was a computational convenience. Not only was the threshold likely to be probabilistic, but in our view even a classical logistic function would have been an oversimplified epiphenomenon of the signal detection problems the animals has of discriminating its internal states of high and low energy flow.

There were more fundamental problems than the characteristics of the function for feeding and non-feeding. Was the same decision function involved in starting and stopping feeding? We formed the impression from data mentioned above that increase in energy supply to tissues at the end of a meal was detectable. For that matter, if homology between physiology and experience has any weight, hunger sensations are easily separated from satiety sensations, and it was reasonable to suppose that these might be experiences of different bodily states, rather than some misreference or illusion generated purely by differences in brain processing. In any case, a single decision function operating on information generated promptly on ingestion might produce unrealistically short meals and intermeal intervals. A positive feedback effect of the taste of food had been invoked by McFarland (1971), Weipkema (1971), Le Magnen (1971) and others, which would serve to lock the rat into feeding behaviour. However, there was no obvious way in which the attenuation of this positive feedback effect, which would largely determine meal size, could be adjusted to relate amount eaten to contents of the gut at the start of eating, the nature of the diet, and other significant conditions. Another possible way of operating with a single threshold was to postulate pretuned oral metering: Toates and Oatley (1969) have a feedforward loop in their thirst model which predicts (from mouth and gut signals by unspecified mechanisms) the eventual parenteral yield of water from the drinking bout. On balance, it seemed to us less arbitrary to think in terms of two thresholds on the same variable, i.e. a starting decision at one level of energy supply and a stopping decision at a higher level of the same energy supply.

We were aware that we were not dealing with the reality of competing motivation and behaviours. With Oatley (1967) and McFarland (1971), we believed that a desire to feed had to interact with other behavioural needs—no doubt weighted according to their biological or psychological functions; and also that several currently strong desires possibly share time in behavioural expression. The combination of this feeding model with a drinking model is described by Toates in Chapter 14. McFarland treates the question of behavioural priorities more generally in Chapter 15, and Booth and Mather refer to some interactions in the human case in Chapter 12. The simulations described in this Chapter treat feeding propensity as rigidly determining feeding behaviour. Some minor inaccuracies and major limitations on predictive range no doubt arise in consequence.

2. *Data on Threshold Absorption Rates*

The type of experiment needed to estimate absorption flows which permit or suppress feeding is not easily performed. (Indeed only now at the time of writing is it being started: a proper design appears even more daunting now the model has been more fully elaborated.) However, we had access to the results which

Campbell and Davis (1974a,b) had obtained in my laboratory in 1971. They showed that short term duodenal or portal (but not jugular) infusion of modest doses of glucose could slow or suppress nutrient ingestion in the rat. From some of their dose-response data using a glucose drinking measure, it was possible to estimate very roughly, a glucose delivery rate which was not quite high enough to affect feeding and another higher rate at which feeding was just about completely suppressed: these were around 15–20 cal/min and 50–80 cal/min respectively.

Such rough and ready calculations from data obtained for other purposes would be worth corroborating from any direction available. The otherwise partly circular move of estimating thresholds from amounts found in the gut at the start and finish of meals did in fact yield estimates in the same ranges. Twelve rats were killed in the second half of the light phase, each as it started to eat a meal undisturbed with free access to chow of energy density 3·43 kcal/g. The stomach contents averaged 0·26 g dry weight, excluding hair and faeces. With a rate constant of 0·6 on a square root stomach clearance function, this corresponds to an absorption rate of 18 cal/min. With a meal size of 2·5 g, stomach contents would approach 2·8 g, which would correspond to an absorption rate of 59 cal/min.

Threshold values of 18 cal/min for feeding onset and 60 cal/min for feeding offset were therefore used in the Mark I version of the modal (Booth and Toates, 1974b; Toates and Booth, 1974).

It should be emphasized that even a procedure of estimating thresholds solely by measuring amounts in the stomach and using the model's gut clearance function would not be viciously circular: the model would only work realistically if the concept of a threshold energy flow were applicable, if constant thresholds could validly be assumed, and if the conditions of stomach sampling were representative of all other conditions being simulated on the basis of the resulting threshold estimates.

The threshold functions are presented diagrammatically in Fig. 3. The procedures include the loop's third component, specification of feeding rate when feeding occurs.

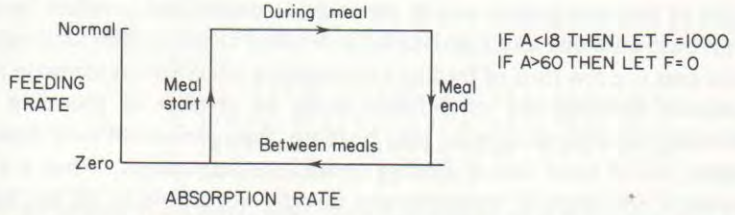

Fig. 3. Double threshold function. Between meals the absorption rate decreases until it reaches the hunger threshold value of 18 cal/min, and feeding is started, at a rate of 1000 cal/min. Absorption rate increases during the meal up to the satiety threshold value when feeding stops.

C. *A Feeding Rate Function*

Given that food is present and that there is a propensity to feed, the simplifying assumption in the present model is that food is taken at a constant rate until there ceases to be a propensity to feed. I believe that in fact the propensity to feed is a consequence of some interaction between internal state and the external situation including sensory characteristics of the food. However, in the situation where there is only one foodstuff, freely available and always presented in the same way, this interaction does not have to be made explicit. The internal state alone (or predictions of it) can determine whether feeding occurs or not. The external situation alone can determine the rate at which food intake occurs. The physical accessibility of the diet (on the floor, in a grid basket, down a tunnel, ease of responding in the case of operant delivery) and the form in which it is presented (blocks, pellets, powder, fluid) can affect the rate of ingestion. Texture, smell and taste (probably in that order) can affect the enthusiasm of mastication and ease of swallowing, both innately and as a result of familiarization and conditioning (Booth *et al.*, 1974) but these effects can be lumped into a constant intake rate with a single diet *ad libitum*. In the rat, there appear to be no systematic data on the effects of different levels of food deprivation or energy flow deficiency on the rate of intake of laboratory maintenance diet.

Constant feeding rate is of course a convenient approximation, but we chose it initially and we have maintained that choice because it appears to be a very close approximation to reality for many situations. Of course, rats do often eat in a series of short phases—mouthfuls, pawfuls, bursts of licking. However, the transit and circulation characteristics of the gut and blood have a considerable smoothing effect. Even if a swallow is sometimes the start of a peristaltic wave extending across the stomach along the intestine, eating bursts within meals probably generate no postabsorptive transients. Major transients at the start and towards the end of meals have also been emphasized by some workers. An acceleration of intake in the early stages of the meal has been observed under some conditions (Wiepkema, 1971; Le Magnen, 1971) and used as a basis for the concept of positive feedback at the start of the meal. Slowing of intake in the latter half of the meal is also widely supposed to occur, and to reflect incipient satiety. However, if one looks at data for individual meals of individual rats, the most one sees is a few runs of feeding at increasing intervals—a stepwise rather than smooth slowing, the smoothness being an artefact of grouping data. Furthermore, the stepped slowing may be more characteristic of fluid diets than solid diets, and of some rats or feeding conditions than others. When a 45-mg food pellet is continuously available and directly accessible to the rat, neither accelerative nor decelerative transients are generally seen in our experience (Table I).

Rates as varied as 0·1 g/min (Le Magnen and Tallon 1966) and 0·5 g/min

Table I.
Interpellet intervals and average feeding rates on the eatometer.

Rat	Day	Phase	Interpellet interval record	Mean feeding rate (mg/min)
		Light	55922 48 33 42 35 45 42 36 30 44 74 32 1 78 60 27 31 41 43 35 55 40 44 64 27 40 44 64 27 40 46	251
	3		51 81 46 37 80 72 24 27 90 65 46 63 82 39 65 42 53 62 52 68 42 41 53 55 45 44 85 36180	
		Dark	18170 12 39 33 49 27 31 27 27 26 37 25 27 29 47 26 27 35 33 40 40 39 27 30 38 52 38 0 41 44 31 481 31 35 28 36 53 28 42 27 39 43 33 43 31 29 37 49 51 34 26 273 61 24 25 42 45 61 24671	264
		Light	46092 61 47 38 44 31 43 42 47 34 61 27 50 98 37 61 28 44 152 83 37 60 136 37 120 49 80 66 140 29 50 83 50 143 44 71 50 54 49 68 38986	215
1	8		23337 36 35 32 54 35 30 28 35 47 30 28 26 40 51 41 81 65 24 33 58 23 253 48 33 46 56 30 31 77 36 69 29 75 95 135 44 132 53 83 29 32 50 856 40 28	
		Dark	88 28 42 31 71 26 25 47 184 27 34 43 53 48 1739 38 60 36 82 35 34 30 46 45 29 39 69 36 54 42 7337 41 32 33 204 57 28 32 35 27 39 62 30 34 31 38 34 14534	194 (156) (169)
		Light	57490 48 42 34 72 30 37 38 33 43 34 43 27 40 33 66 33 35 37 36 50 71 42 31 53 29 59 25771	295
	9	Dark	16246 33 45 37 50 26 46 34 38 39 31 31 35 47 39 21 32 35 38 40 36 38 37 63 28 46 35 46 36 29 9682	317
		Light	37402 52 45 32 35 39 33 22 38 38 29 31 35 36 35 18 31 35 1420 26 46 16 36 47 33 34 28 32 28 34 27 31 33 32 21 38 44 37 35 37 22 36 55 31 26 85	205
4	4		37 35 30 42 53 39 40 19148	
		Dark	14076 18 52 49 29 37 40 31 57 26 33 40 43 18 31 41 41 30 34 43 34 35 45 31 36 32 46 29 39 374 28 40 41 53 25 38 30 43 42 950 15 53 18 50 66 14 63 15 168 108 28 26 21 38 35 46 49 31 103 35 6192	207
		Light	37288 69 55 62 50 51 38 116 53 38 33 54 44 31 34 49 44 48 30 115 20 29 46 37 40 48 64 61 32 22772	255
7	5		16832 76 34 36 34 44 59 26 30 95 27 45 25 47 33	
		Dark	42 30 41 62 55 31 131 33 43 47 53 31 34 54 36 50 27 54 43 54 46 42 55 53 44 30 44 7313 55 35 33 43 51 30 36 45 23 51 18243	285 (75)

Intervals between 45-mg Noyes pellets taken were printed out in 0·2-s units, with 1·0 sec of dead time for printing. Thus a printout of 45 corresponds to 10 s and a local rate of 270 mg/min. The meals just before midnight and midday respectively are tabulated with their pre- and postmeal intervals from such a record which had no built-in criteria (Booth and Campbell, 1976).

(Levitsky, 1970; Kissileff, 1970) have been reported, but around 0·3 g/min is typical with pellet eatometers and for many laboratory maintenance diets in block or powder form (Table I; De Castro and Balagura, 1975). The feeding rate in g/min or ml/min has to be multiplied by the energy density of the diet in cal/g or cal/ml respectively for the purposes of the model. Some lab chow is quoted as 3·2 kcal/g (Le Magnen and Devos, 1970), other chow at 3·43 kcal/g (Booth, 1972a). When gastric distension is modelled, water content of the diet can be ignored (except when water intake is being modelled, as in Chapter 13) on the assumption that salivation and gastric secretion even up the differences between dry and wet diets. In SI units, our values for standard chow, where better are not available, are 5 mg/s intake weight rate and 13·4 J/mg energy density. This corresponds to an energy intake rate of about 1 kcal/min.

D. *Performance of the Loop*

This elemental model (Fig. 4) was bound to produce meals, because of the double-threshold component. So long as clearance during the meal proved not to be disproportionately great, we also expected meal sizes to be fairly realistic, because of the cross-checking we had done in the thresholds data bases and because absorption was modelled as instantaneous. The prediction of interval between meals was less trivial, because (once the feeding onset threshold was set) the inter-meal interval was critically dependent on the gut clearance function. The model's inter-meal interval for a 2·5-g meal was in fact 230 min (gut rate constant 0·6; absorption onset and offset thresholds 18 and 60 cal/min; eating rate 0·3 g/min; chow density 3·2 kcal/g).

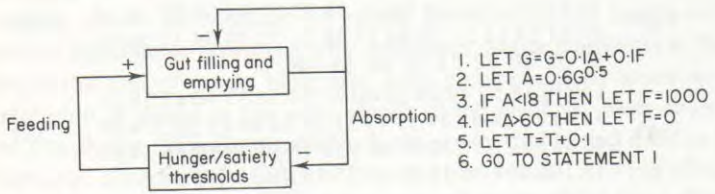

Fig. 4. The elemental loop of absorption from the gut, an energy-flow thresholds system, and entry of food into the gut. The calculation cycle is outlined in the list of statements to the right, where G is gut contents A is absorption rate and F is feeding rate (as in Fig. 2), and T is time in minutes. The 6-s interval between calculations, as well as substantive parameter values, can be reset if better values become available.

We proceeded then to consider elaborations and perturbations of the elemental loop. The first question we set ourselves was whether known perturbations would account for the circadian variations in the rat's meal pattern. We also considered what perturbations might produce the currently studied changes in

food intake and feeding pattern induced by manipulations such as damage to the hypothalamus or to the pancreas or physiological changes such as rise or fall in environmental temperature.

III. Circadian Pattern

A. *Variation in Gut Clearance Rate*

Jarman's data on the passage of a glucose load through the gut had clearly shown that the rat's stomach empties considerably faster in the dark phase of the lighting cycle than in the light phase (Booth and Jarman, 1976). We expected the incorporation into the model of this daytime reduction in the value of the gut clearance rate constant to lengthen the time that the system would take for rate of absorption to fall from the satiety threshold to the hunger threshold during daylight. That is, the model should at least make a prediction in the correct direction, that meals are less frequent by day than by night in the rat. The question was how much more or less of a day–night difference would be predicted by this computation than is in fact observed, and what other effects the gut clearance variation might have on the meal pattern, e.g. on meal size. Any progress in this direction would provide an interesting comparison with the Oatley—Toates modelling of drinking in the rat. There they found it best to simulate the circadian drinking pattern by a set-point change. Here a major contribution could be made by a peripheral processing change. However, there was and is a difficulty with modelling circadian variation. The feeding rhythm observed appears to be quite sensitive to the conditions of housing, as well as no doubt being affected by differences in strains etc. Even laboratories all using a cycle of 12h dark and 12h light report a wide range of ratios of night-time intake to daytime intake, varying at least from 1·5:1 to 3:1. Possibly the main variable in this is how much the animals are disturbed by extraneous stimuli during the light phase (Booth and Campbell, 1976). Night/day ratios tend to be higher in reverse-cycle conditions than in conditions were the nocturnal rat has to compromise with diurnal human beings.

In fact, a change of gut clearance rate constant has several consequences even in the elemental model. The daytime slowing does increase the ratio of intermeal interval to size of the preceding meal. It also increases the amount in the stomach at the start of a meal, because the absorption rate low enough to release feeding corresponds to a greater gut energy contents when the rate constant is lower. This makes it a greater strain on the mathematical intuition to anticipate ahead of computation whether meal sizes will change much from night to day: if stomach contents at the start of meals were the same by day as by night, then modelled daytime meals would certainly be bigger—because the lower rate constant would require a larger gut content to reach an absorption rate high enough to

switch off feeding. The higher starting contents and the nonlinear relationship between gut contents and absorption rate makes a simple non-mathematical scientist like myself turn with relief to a programmed calculating machine. How important is the clearance during the meal? How critical are the values of hunger and satiety thresholds we have chosen?

At an eating rate of 1 kcal/min (i.e. about 0·3 g/min), hunger and satiety thresholds of 18 and 60 cal/min and gut rate constants of 0·9 by night and 0·6 by day (derived from Jarman's glucose data), the model predicts 1·5-g meals at 110-min intervals by night and 2·5-g meals at 245-min intervals by day.

B. *Variations in Thresholds*

We had yet to incorporate another substantial known circadian influence in the elemental loop (see Section III C), but we paused to consider a qualitatively unrealistic aspect of this prediction. Meal sizes are occasionally found to be almost identical by day and by night in the rat. Usually night-time meals are somewhat larger than daytime meals, e.g. mean values in the range 2·5–3 g as opposed to 1·5–2·5 g by day. We were not aware of any report of smaller meals by night. Introducing the gut rate variation had produced predictions of the right order in other respects—meal sizes and intermeal intervals in the right ranges, and a meal size/intermeal ratio difference between night (0·014) and day (0·010) in the right direction. What was wrong with the simulation of day–night difference? Did something else vary that was already represented in the model, or was there another factor determining meal size which was yet to be represented? We were not too concerned about this failure at this stage, for two reasons. Firstly, the failure was only partial: the predicted total intakes by day and by night were close to reality, i.e. meals were timed appropriately for their size. Secondly, larger meals by day seemed at the time to be the right prediction in the context of ventromedial hypothalamic hyperphagia (Section III. C. 1.b.(ii)).

In the light of his thirst modelling, one possibility was obvious to Toates: maybe the hunger threshold or the satiety threshold or both thresholds varied between night and day. He found that in simulations only the satiety threshold value was critical for meal sizes, although varying the hunger threshold did have some effect. However, both satiety and hunger thresholds were critical for intermeal intervals. So if we introduced the complexity of a circadian variation in satiety threshold to explain the usually observed day–night meal size difference, the intermeal intervals were changed too—smaller daytime meals meant smaller meal size/intermeal interval ratios by day, and the circadian feeding rhythm almost disappeared altogether! If thresholds were varying, the elemental model had to include a reduction in both thresholds to produce smaller meals by day with high size/interval ratios. Could behaviour be hard to get going and easy to stop by day when the rat is less active and more sleepy? In the absence of

either direct evidence or strong theoretical conviction, we were not disposed to establish such a postulate in the model at this early stage. Later I found it was unnecessary anyway (Section IV. B. 2. a).

Nonetheless, we anticipated that one day the threshold functions would have to be elaborated to permit motivational interactions. Feeding may have to share time with sleeping, especially by day. Feeding and drinking may compete at times during meals, It appears from Oatley's (1971) result and Toates' simulation of combined feeding and drinking systems (Chapter 14) that the circadian drinking rhythm is not purely secondary to the feeding rhythm. It is not clear yet whether the primary drinking rhythm is an aspect of an arousal rhythm or a variation to some extent specific to thirst. More precise data to determine the components of the full model of feeding may yet revive the question of circadian threshold variation in the energy-based system.

C. *Variation in Metabolic Diversions of Absorbed Energy*

The theory that energy supply controls appetite does not permit one to be restricted to the flow of energy from intestinal absorption. Variations in absorption rate will affect a feeding control system only relative to variations in other energy flows, in particular the consumption of energy by all tissues in the body, or all except perhaps the energy flow detector cells themselves. However, energy is not only converted to external work and to heat, but is also converted to potential energy, predominantly as triglyceride fat. Elaboration of the debit and credit accounts for loss, storage and release of energy were a major part of successive extensions to the elemental model just described.

1. *Circadian Lipogenesis–Lipolysis Rhythm*

(a) *Energy flow and the fat store.* If one entertains the hypothesis that hunger and satiety reflect energy supply with little regard to substrate, then for consistency one should suppose that energy released from storage will add to energy absorbed from the gut to inhibit feeding. This deduction from an energy flow hypothesis has an attractive corollary: if the tendency to mobilize fat increases at all as the amount of fat stored increases, then a powerful mechanism for stabilizing body fat content exists. This would avoid postulating more complicated or more accurate fat-measuring devices such as some proposed in recent years. It would be neatly symmetrical to assume that deposition of fat subtracted from the absorptive energy flow and so attenuated satiety. At the time we were building the first version of the model, Le Magnen kindly provided an advance copy of the paper from his laboratory on short term measurements of oxygen consumption and carbon dioxide production which illustrated the correlation between frequent, larger meals and net lipogenesis and less frequent, smaller

meals and net lipolysis (Le Magnen *et al.*, 1973). By making some conventional although approximate assumptions, Le Magnen and Devos (1970) had estimated the net rate of energy flow into fat synthesis or from fat mobilization over a given period of time: this involves calculating from the proportion of carbon dioxide production to oxygen consumption how much oxidation energy the rat was deriving from food and how much from fat over that period. Le Magnen *et al.* (1973) calculated the night-time total excess in energy intake from the cumulative diversion of energy into lipogenesis and a largely compensatory total deficit in daytime intake permitted by mobilization of that energy excess. Our model provided a way to use Le Magnen's data more precisely, relating each short term estimate of lipogenesis/lipolysis to feeding behaviour occurring at the same time.

Many radioisotope incorporation studies show that a re-fed animal moves promptly to fast fat synthesis, and human respiratory calorimetry has shown the shift from preprandial net lipolysis to postprandial net lipogenesis. We would expect the same rapid changes around meals in the rat. Le Magnen and Devos (1970; Fig. 11) provided some 20-min average estimates indicating shifts towards faster lipogenesis after meals, although the results were not sufficiently complete for use on our model nor arithmetically well matched to their other data in the same paper. The bulk of the data published from Le Magnen's laboratory consisted of 2-h averages, unfortunately lacking the temporal resolution or more particularly the meal relatedness that our model's absorptive flow calculations had. However, the data did represent the smoothed trends in the circadian variation from lipogenesis by night to lipolysis by day. The 1973 paper presented respiratory data for a greater number of animals than the 1970 paper, but when the equations of Le Magnen and Devos (1970) are applied to

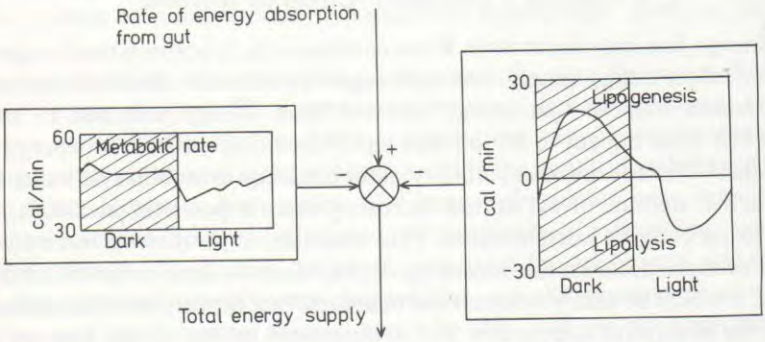

Fig. 5. Metabolic components of the energy flow summation. Mark 1 included only lipogenesis–lipolysis ("lipoflow"). Mark 2 included metabolic rate in the calculations as well. The curves represent estimates made by Le Magnen and Devos (1970) from respiratory data averaged over period of 2 h around the clock. The computer programs used linear interpolations between the mid-2-h data points originally reported.

the 1973 data a much more modest circadian rhythm of lipogenesis–lipolysis is seen. We decided to represent as strong a circadian rhythm of fat storage and mobilization as had been evidenced, therefore taking Le Magnen and Devos (1970) 2-h averages around the clock and adding an interpolated value for the appropriate time of day to the absorptive flow estimates with the model (Fig. 5).

This addition was rather absurd as the absorption calculation was updated every 10s in our model, and the estimated flow often changed more in a few minutes than the highly smoothed 2-h average lipogenesis–lipolysis estimate did in hours. We consoled ourselves with the thought that this was another component whose values were soundly based on data, and that its inclusion gave the model a chance to reflect a general tendency that varied around the clock. In fact, the lipogenesis–lipolysis cycle helped to correct the disparity in meal sizes in the wrong direction between night and day that was introduced into the elemental model by the circadian variation in gut clearance rate (Fig. 6). However, later simulations in the Mark 3 version showed this to be a misleading viewpoint.

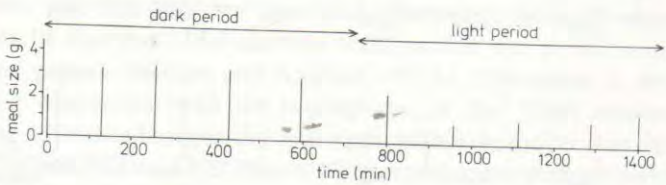

Fig. 6. Meal pattern on a representative day when the circadian lipoflow cycle is included in the calculations, but no circadian variation in the gut clearance rate factor (constant at 0·75 throughout the 24 h). (This is not a realistic simulation as lipoflow variation is likely to be strongly dependent on gut clearance variation. It is intended only to indicate the relative contributions of lipoflow and gut clearance rhythms when compared with Fig. 7A and C).

(b) *Feeding model: Mark 1.* At this stage we thought the model had become interesting enough to submit a brief account for publication and to talk about it at meetings (Booth, 1973; Booth and Toates, 1974a, b). Our first summary was eventually judged too specialized for a general science journal or a local psychological journal and so Jack Davis kindly sponsored it in the Psychonomic Society bulletin (Booth and Toates, 1974b). This had the spin-off that Davis programmed the model from our brief verbal account and got exactly the same results—so we had the comforting assurance that we had at least been programming what we intended to. Later in the year, *Nature* took a brief account with a more general introduction and several additional types of simulation included (Toates and Booth, 1974).

This simple model had a considerable predictive range. If available observations or reasonable assumptions were applied to specify the states of components

of the system, the model made quantitative predictions over the conditions now listed. The predictions were generally in approximate agreement with reality, which was even more encouraging.

(i) Intact rat. The envelope of the lipogenesis–lipolysis rhythm was neatly reflected in the meal sizes and intermeal intervals of a simulation of the freely fed rat (Fig. 7). As lipogenesis intensified in the dark, so meals increased in size and came closer together. Conversely, as lipolysis increased during the light period,

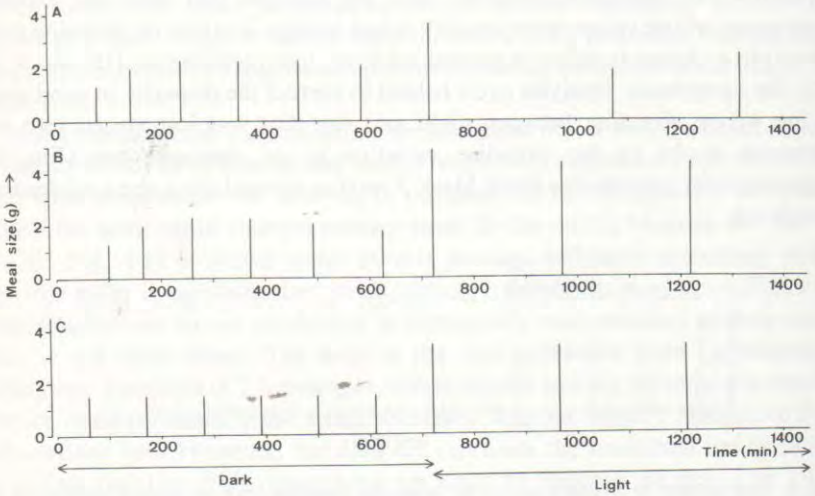

Fig. 7. A, Intact rat. B, Ventromedial hypothalamic lesion—dynamic phase (daytime lipoflow lipogenic as at night). C, VMH static phase (no net lipoflow at any time). These are meal pattern predictions from day 2 of computer runs whose day 1 outputs were given in fig. 2 of Booth and Toates (1974b). The day 1 outputs always started with a meal as the simulations were set with an empty stomach initially.

meal size decreased and the meal-to-meal interval (already lengthened by slowed gastric clearance) increased. Total intakes by day and by night were in the right range, and so long as the relation between meal size and meal-to-meal interval differed in the correct direction also between night and day, we were less concerned that daytime meals were still predicted wrongly to be larger than night-time meals. Despite the variation imposed on the effects of constant gut rate by the circadian fat rhythm, the variance of meal size was unrealistically low. Again, this was attributable to a conveniently but arbitrarily deterministic model and so did not bother us. The sudden slowing of gut clearance at dawn precipitated meals unrealistically close in time to change of lighting. We therefore decided, rather than change the value of the gut rate constant instantaneously at dawn and dusk (which was unlikely to be realistic), to allow

the value to change linearly over an hour before and an hour after lighting changeover. Data on the time course of shifts in gastric clearance rate around lighting changes are now being obtained (Newman and Booth, in prep.).

(ii) Rats with ventromedial hypothalamic lesions. Rats with bilateral destruction of the area of the ventromedial nucleus of the hypothalamus do most of their well known overeating and extra fat deposition in the light phase (Balagura and Davenport, 1970; Kakolewski *et al.*, 1971; Le Magnen *et al.*, 1973). Indeed, Le Magnen *et al.*, (1973) had respiratory data indicating a constant high level of lipogenesis around the clock. We simulated VMH lipogenesis either as a daytime repeat of the night-time lipogenesis reported in the intact rat by Le Magnen and Devos (1970) or on the basis of their 1973 data.

The daytime lipogenesis almost doubled the food intake total predicted by the model for that period. However, this was not as large an intake as reported by Le Magnen *et al.* (1973), and so it seemed likely that some additional factor(s) also contributed (see Section IV.B.2.b.). The model predicted that the greater intake was achieved by a great increase in daytime meal size, with a slight decrease in intermeal interval (Fig. 7B). Our impression from Le Magnen's report was that this was not unrealistic. However, Kissileff assured us at Ermenonville that the VMH daytime meal pattern was in fact similar to the night-time pattern (Becker and Kissileff, 1974). This made it obvious that something was wrong with the assumptions of this VMH simulation. The remaining difference between day and night, within the model, was the values of the gut rate constant. Over the coming months we were to formulate the hypothesis that a major abnormality following VMH lesions was the loss of slowed clearance by day (Booth *et al.*, 1976; see Section IV below).

The elemental loop without net lipogenesis or lipolysis was reincarnated by Booth and Toates (1974b) as a simulation of the static phase of the VMH syndrome (Fig. 7C), in which the animal's obesity has reached a plateau and total food intake is practically normal, although the intake ratio between night and day remains abnormally near unity. The accumulation of now unacceptable assumptions in the components of this simulation (Section IV.B.2.b.) make it seem even more of a joke now than it did initially.

(iii) Rats with lateral hypothalamic lesions. We ran simulations with much slower feeding rates (Toates and Booth, 1974). These might have reflected at least some aspects of the lateral hypothalamic syndrome—in particular, the apparent aversion to food even when the initial loss of sensory reactivity in this preparation has attenuated, and also the abnormal tendency to drink frequently during meals which persists even when the lateral rat has otherwise fully recovered from its initial failure to eat. Given the absorption smoothing effect of gastrointestinal processing, we assumed that there was no need to represent in the model the distinction between slow uninterested feeding and much interrupted feeding.

With a net feeding rate as low as about one-tenth of normal, the model never stopped eating during the night and hardly ate at all by day. This has a qualitative similarity to the recovered lateral rat. At less severely reduced feeding rates, the meal sizes and intervals between meal starts were more normal, although of course meals took much longer and intermeal intervals were reduced.

Once again, simulation with only one component changed is not a fair test of the fully developed model's power to explain a real syndrome. Use of a normal lipogenesis–lipolysis rhythm was obviously likely to be incorrect. Later there appeared good reason to simulate the recovered lateral hypothalamic rat as also suffering from an increased metabolic rate (Keesey, 1976) and from a slowed stomach (Booth, 1976; notwithstanding the results of Ralph and Sawchenko, 1975), with liquid diet, which can be misleading.

(iv) Food intake after food deprivation. A rat deprived of food for a period such as 6–24 h eats a larger than average meal when access to food is restored, and returns to take a second meal sooner than a freely fed rat would do on average. An adjustment in the lipogenesis–lipolysis input to the model was sufficient to stimulate these effects: if a meal started at the fastest observed level of lipolysis (10 cal/min) and this was changed over about half an hour to the highest level of lipogenesis and maintained at that level (35 cal/min), then a larger meal (4·0 g) and shorter meal-to-meal interval (116 min) than the *ad libitum* average was predicted (Booth and Toates, 1974b; Booth *et al.*, 1976), real rats taking 4·0 g followed by 110 min (Le Magnen and Tallon, 1968).

However, this simulation mainly served to sensitize us to the need for further additions to the model. If switches from lipolysis to lipogenesis around meals were to be represented, they should also be included in the simulation of freely fed rats. Also, rats which are repeatedly deprived according to a schedule show a steady increase in size of the first meal when access is restored (Le Magnen and Tallon, 1968). Deprivation schedules augment lipogenic capacity (Cohn and Joseph, 1960), but even this further adjustment of the fat synthesis component of the simple model (Fig. 8) would not produce realistic predictions: rats

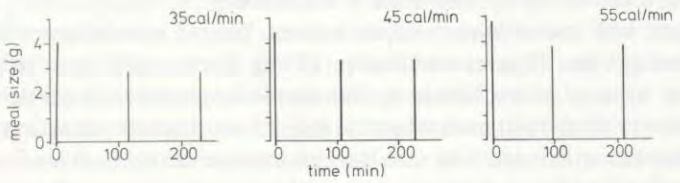

Fig. 8. Simulations of the meal pattern following food deprivation. Lipoflow was taken to be 10 cal/min of lipolysis at the start of the meal in all cases, but to rise shortly after the meal to lipogenic asymptote of the value indicated in each case. Greater lipogenesis causes larger meals, but the effect on the first meal is very modest compared with the 6–10 g meals typical on restoring food to a rat which has been adapted to the deprivation schedule.

adapted to deprivation schedules take a first meal of 6–10 g. If the model was along the right lines at all, a major component was missing—such as perhaps learned behaviour as well as adapted physiology (Section IV A).

(v) Insulin-induced eating. The increase in food intake elicited in the rat by injection of a large dose of insulin (Booth and Brookover, 1968; Steffens, 1969a) is generally attributed to a failure to support glucose metabolism (cytoglucopoenia) in the brain during insulin-induced hypoglycaemia. However, as Le Magnen and Devos (1970) and Le Magnen *et al.*, (1973) emphasized, the possible contribution of the large lipogenic effect of the insulin injection must be considered. This is part of the cause of the hypoglycaemia, of course, and so this consideration may prove only to treat the problem of insulin-induced eating at another level of analysis—total energy distribution rather than purely glucose distribution. Nevertheless, such an analysis of the phenomenon brought it within the range of the Mark 1 model: set at a temporary high level of lipogenesis, it could make a prediction as to the effect of insulin injection on feeding. This simulation was qualitatively identical to simulating the dynamic phase of the VMH syndrome as in (ii) above. Overeating was predicted in the light phase but not in the dark phase (Fig. 7B)—unless the already strong night-time lipogenesis was supposed to be further intensified. In fact we had just obtained data, later published by Booth and Campbell (1975) showing that insulin does induce additional food intake at night in the rat, although the effect is more modest than by day. This finding was not consistent with a view that insulin induces feeding by reversing net lipolysis to net lipogenesis, but it was accommodated by an interpretation that insulin adds a lipogenic tendency to pre-existing net lipolysis or lipogenesis, except on occasions when lipogenesis is already maximal as it sometimes probably will be at night in the freely fed rat.

Quantitative simulation of the lipogenic effect of insulin to predict its effect on food intake had to await realistic modelling of normal periprandial lipogenesis by day and night, just as with deprivation effects. If increased lipogenesis did prove to explain insulin-elicited eating, this would support the view that the phenomenon can be regarded as an unphysiological acceleration of postprandial nutrient processing (Booth and Pain, 1971), while satiety-augmenting effects of smaller doses better represent the physiological role of insulin in feeding (Lovett and Booth, 1970; Booth and Jarman, 1975).

(vi) Variation in heat loss. A simulation of control of feeding by net energy flow to a satiety/hunger receptor system readily accommodates semi-quantitative predictions of the effects of increased loss of energy by the demands of exercise or of temperature maintenance in the face of reduced environmental temperature, or conversely a reduced cost of thermoregulation when the environmental temperature is raised to a modest extent.

For example, we calculated the effect of subtracting a constant drain of 5 cal/min in the Mark 1 model, or adding a constant economy of 5 cal/min (Table II).

Table II
Feeding model Mark 1: percentage changes in food intake on change in energy losses

	Change in metabolic rate	
	Up by 5 cal/min[a]	Down by 5 cal/min[b]
Amount eaten in light	+18%	−33%
Amount eaten in dark	+7%	−10%
24-h intake	+11%	−18%

[a]Cf. moderate exercise or cooling.
[b]Cf. warmer environment.

The purely behavioural effect of subtraction by heat loss is of course identical to subtraction by increased lipogenesis, as with insulin injection. "Cooling" or "exercise" increased intake substantially, "warming" decreased it. In reality, the behavioural picture is complicated by varying time courses of such changes in food intake. Effects not well enough understood to be readily incorporated in a model include the transient hyporexia following vigorous exercise (Baile *et al.*, 1971), the stress of rapid large change in external temperature, and the energy costs of different ways of keeping cool in very warm environments.

Again, the most important effect of running these variations on Mark 1 was to focus our attention on a missing component—a general representation for heat loss. This was incorporated in subsequent marks (Section III. C.2a).

(vii) Diabetes mellitus. In chronic diabetes, large amounts of energy are lost as sugar and other substrates in the urine. Nevertheless, there are substantial amounts of energy circulating to the tissues as glucose, amino acids and ketone bodies. Booth (1972b, c) provided evidence that the large food intake generally seen in chronically diabetic rats was attributable to a satiety deficit—the rats did not respond to the postabsorptive action of glucose loads, and they showed an abnormally low proportion of longer time intervals between meals. The reduced meal sizes seen by Booth (1972c) are not typical of experimental diabetes mellitus (Panksepp, 1973; De Castro and Balagura, 1975), and after that report was published the food pellets were found to have been formulated using industrial spirits and to be aversively bitter. The diabetogenic drug was streptozotocin rather than alloxan, whose destruction of pancreatic beta cells is more extensive while its specificity is less; the rats were also eating considerably more than De Castro and Balagura (1975) report: so the ketoacidosis they invoke is less likely to have reduced meal sizes than the poor acceptability of the diet, especially given the slowing of feeding rate which occurs in any case in diabetes (Booth, 1972c; De Castro and Balagura, 1975). The satiety deficit interpretation is not dependent on any correlation between meal size and interval to the

next meal; indeed Booth (1972c) reported the loss of the modest correlation which appeared before injection.

Large meals and relatively reduced intervals between meals were indeed predicted by a simulation of the diabetic satiety deficit as a failure of absorbed energy to have its full effect plus a failure ever to deposit fat—indeed a continual mobilization of fat as the scrawniness of chronic experimental diabetes develops (Table III). However, the meal sizes were impossibly large—30 g of food (with a

Table III
Model Mark 2 and 2D: feeding in a diabetes-like state

	Total 24-h intake (g)	Number of meals	
		Light	Dark
Without distension	90	1	2
With distension	63	2	4

Effective energy flow from gut = 0·3 of actual flow. Lipolysis = 10 cal/min (constant). Cited by Toates and Booth (1974) and Booth and Toates (1974b).

similar volume of fluid) would literally burst the rat's stomach if it actually went in. This seemed an obvious context in which to invoke the interpretation of gastric and/or intestinal distension as a safety mechanism, high in threshold and not normally operative. We decided to add a loop which represented an inhibition of feeding when gut contents became very large in volume. Russek (1971) had suggested that distension elicits a reflex breakdown of liver glycogen via sympathetic innervation, in which case the mechanical stimulus was indirectly producing an energy flow at the liver. Even if this was not the case, it was computationally convenient to represent the inhibitory effect of distension as an energy flow, if only "virtual" not real.

Unfortunately, we could find no experiments in which gastric (or intestinal) volume had been measured while an inhibitory effect on feeding behaviour was measured in the absence of possible postabsorptive consequences of the gut manipulations. The simplest procedure we could think of was to take Paintal's (1954) neatly linear relation between larger values of stomach volumes and firing in vagus nerve afferents in the cat and assume that the vagal firing was in direct proportion to the satiety effect. We divided the volumes by ten to scale down the cat to the size of a rat. We assumed that the prevention of feeding by gastric distension acting alone would arise near the physical limit, i.e. around 40 ml. This gave the distension satiety function of Fig. 9. We believe that the direct satiating effect of distension is very small except under conditions of large meals. Also the data base is behaviourally inadequate and the physiological mechanisms remain indeterminate, and so the distension loop rather spoils the

philosophy of the rest of the model. Therefore we omit distension, except when specifically mentioned. Another way of rationalizing this strategy is to profess the suspicion that the volume threshold is considerably higher than even the 5 ml in the model loop of Fig. 9. An increase in slope to compensate for a higher threshold would produce broadly similar predictions in many circumstances.

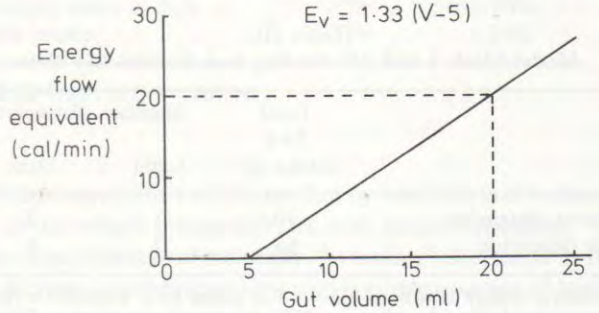

Fig. 9. A satiating influence of gut distension at high threshold. Distension-induced satiety is represented in the calculations as equivalent to a real flow of energy to the hunger/satiety receptor system.

Table III shows predicted meal sizes became more than moderate when the distension loop of Fig. 9 was incorporated in this primitive model of diabetes. A less drastic attenuation of the satiating effect of absorption, plus an adjustment in the energy loss component added in the next Section, would produce still more realistic meal sizes.

(viii) Dehydration anorexia. Toates began to relate the Toates–Oatley simulation of thirst physiology to the hunger model, by representing any water deficit calculated in the drinking model as an inhibitory influence on feeding—for convenience as "virtual energy" like the representation of distension satiety anorexia. This model marriage, and its children, are presented by Toates in Chapter 14.

2. *Circadian Metabolic Rate Rhythm*

(a) *Lumped estimate of energy consumption in non-receptor tissue.*

(i) Short term metabolic rate. Heat loss is a very large flow of energy which has to be supplied by the animal from absorption, fat mobilization, and sometimes other endogenous energy supplies. However, the loss is relatively constant and so it was not represented in the Mark 1 model. Nevertheless, even as background diversion of energy from the satiety/hunger receptor system, it could not be ignored entirely, because circadian variation was clearly observable

in the data from Le Magnen's laboratory. The cause of this variation bears further analysis—and receives some later in the chapter. But at this stage we wanted to make use of the metabolic rate data since they were available from Le Magnen's respiratory exchange data exactly in parallel to the lipogenesis–lipolysis estimates. Inclusion of metabolic rate, i.e. heat output, would also enable calculation of the model's energy balance, by difference from energy input as food. Le Magnen's lipogenesis–lipolysis cycle gave a small cumulative fat gain over 24 h. The cumulative difference in feeding rate and metabolic rate gave a total energy gain, and the difference between total gain and fat gain was an estimate of non-fat energy gain, which approximates to lean body mass growth.

Le Magnen's 2-h average metabolic rate estimates around the clock were therefore subtracted from the sum of absorption and lipolysis (Fig. 5). Strictly logically, we should probably take 99% or some large fraction of metabolic rate, which is heat flow to the environment, to represent energy lost by all tissues except the receptor cell itself—if the assumption is correct that the system looks at its energy input and not its net energy supply. However, we assume that this correction, if appropriate at all, would be negligibly small.

(ii) Threshold values. The original hunger and satiety thresholds were estimates of absorption rates at which feeding was begun and suppressed, against a hitherto unspecified background of lipogenesis–lipolysis and heat loss. When a background metabolic rate of about 35–40 cal/min and a modest few cal/min of lipogenesis were subtracted from the Mark 1 threshold values of 18 and 60 cal/min, the hunger and satiety threshold values became about equal and opposite in sign, around −20 cal/min and +20 cal/min respectively. The infusion data and the gut contents data on which the absorption threshold estimates were based had margins of error of at least five cal/min either way. Furthermore, the estimates of metabolic rate came from another laboratory, different in strain of rat, type of chow and the housing conditions for the experiments. So the data base had a degree of approximation which permitted modest indulgence of predilections for symmetry and for nicely rounded numbers. There was also the general theoretical preconception that organisms like rats might build their feeding control around the detection of decline in energy supply and of incipient excess in energy supply. Such an organism need have only one type of detector system, namely one that is inactive when its energy supply is in a null range, but triggers feeding when the supply gets noticeably low and stops it once supply becomes rapid again. Such a detector could well have thresholds which were symmetrical around a net zero flow of energy into the type of tissue in which it is contained.

The particular threshold values chosen do of course have a substantial effect on details of meal size and intermeal interval (Table IV). However, a few cal/min in either direction leaves the meal size predictions within the range of means reported from different laboratories. There is little effect on total food intake or

cumulative increase in body energy contents so long as the threshold values are varied symmetrically around zero. However, daily intakes and energy increments are sensitive to changes to threshold values which are asymmetic around zero (Table IV, bottom half).

Table IV
Model Mark 2: Effects of various hunger and satiety threshold values

Thresholds (cal/min)		Amount eaten (g)		Approx. meal size	Number of meals		24-h energy increment
On	Off	Light	Dark	(g)	Light	Dark	(cal)
−20	20	7·5	16·3	2·4	3	7	4500
−15	15	7·7	15·3	1·7	4	9	4000
−25	25	7·0	17·1	2·9	2	6	6500
−30	15	4·5	14·6	2·0	2	7	−8360
0	40	12·2	22·6	3·0	3	7	34 000
0	25	11·7	19·7	1·8	5	11	30 000
−15	10	7·2	15·2	1·5	5	11	1280

Cited by Booth and Toates (1974b) and Booth *et al.* (1976).

Threshold values are less adequately specified by experimental data than are many other components of the model. On the basis of the above considerations we decided (until such time as better data were available on energy flows at the start and end of meals) to use threshold values approximately symmetrical around zero net flow of energy to the non-lipid components of parenteral mass, and in the region of 20 cal/min or slightly less. These values were compatible with the fragmentary data directly available. They were also compatible with data indirectly, in that they kept reasonably realistic the predictions from a whole model in which the other components were fairly tightly data-determined.

(b) *Feeding model: Mark 2.* The addition of metabolic rate and the energy accumulation calculations, with the distension loop if desired (Mark 2D), yielded a version of the model which was presented at the Jerusalem and Los Angeles hunger conferences near the end of 1974 (Booth and Toates, 1974c; Booth *et al.*, 1976). As well as collaborating in the incorporation of literature data into the model, Toates had carried out all the computations cited above while he was in Odense. He was then interrupted by the turmoil of a move in the summer of 1974 and I had the help of Steve Platt to write a program for the Mark 2 version of the model to run in Birmingham. Fig. 10 gives a block diagram of Mark 2D, with the key equations from the computer program to which it corresponds.

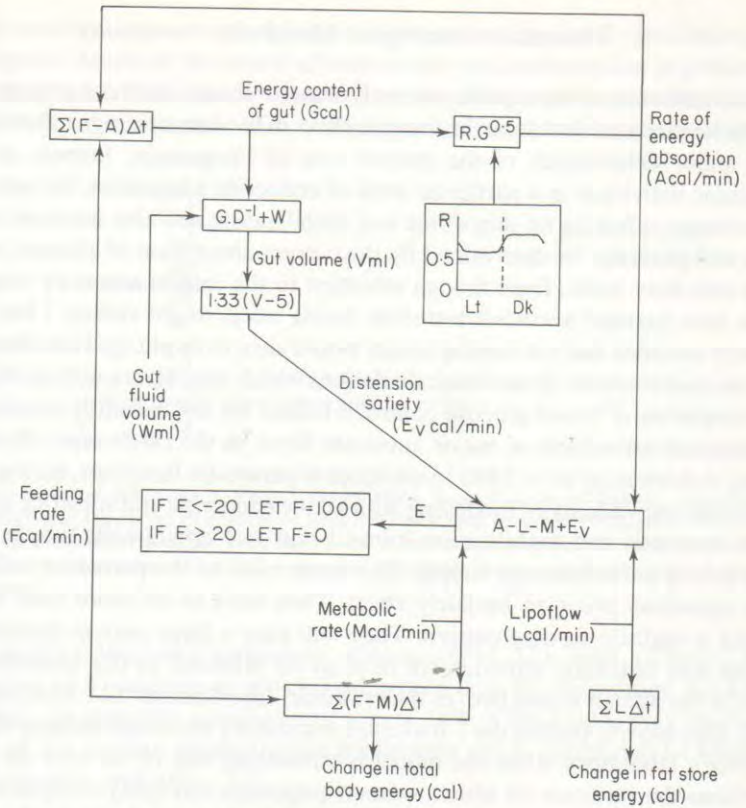

Fig. 10. Feeding control model. Mark 2D. E is the net rate of energy supply (cal/min) to non-lipid parenteral tissues which contain the hunger/satiety receptor system; other symbols are defined in the diagram. $\Sigma \times \Delta t$ is an approximation to integration carried out by successive additon at short intervals of simulated time.

(c) *Derivation of metabolic rate from other data.* If one is able to specify the environmental temperature, the rat's body weight, the amount of exercise it is taking, and the heat lost by processing its diet, it is possible to estimate metabolic rate from known empirical equations (Wunder, 1975). At the time of writing, we do not go all the way down this path, even with the Mark 3 simulations, because useable activity data are not generally available. It is qualitatively clear, however, that rats are much more active in the dark than they are in the light, relatively independently of feeding schedule and type of caging (Norton *et al.*, 1975). This factor probably dominates the increase in metabolic rate by night. Faster processing of food and hence an average higher thermic effect ("specific dynamic action") is a relatively minor contribution. In line with Le Magnen's data, we generally add an activity increment of about five cal/min to the metabolic rate at night over the daytime rate.

3. *Absorption-contingent Metabolic Variations*

The current rate of absorption not only should determine the component of metabolic rate attributable to the thermic effect of food processing, it should also be a major determinant of the current rate of lipogenesis. Indeed, given a particular individual in a particular state of endocrine adaptation, the secretion of hormones affecting fat deposition and mobilization and also increase in lean mass will generally be determined by the current absorption of glucose, amino acids and fatty acids. Even though attention to the insulin secretory response alone, plus perhaps hormone secretion during sleep, might suffice, I had until recently assumed that the feeding model would have to be plunged into details of enzyme and hormone dynamics (calculations which after all are well established for simulation of blood glucose control). Indeed we are currently engaged on biochemical estimation of major substrate flows in the rat *in vivo*. However, noting Ackerman *et al.*'s (1965) experience of parameter lumpings, during 1975 I explored the viability of modelling with all the endocrine and substrate control of fat synthesis and mobilization lumped into two appallingly simple linear functions of current energy supply. The constraints on the parameter values in such equations prove to be fairly strict. They have to do more than merely predict a realistic feeding pattern. They will play a large part in determining growth and fattening, although we have so far attended to this consideration more in the human model than in the rat model (see Chapter 12). Most directly of all, they have to predict the 2-h average respiratory exchanges measured in Le Magnen's laboratory when the model is simulating rats of the type he used.

I chose the variables on which to base lipogenesis and lipolysis equations on the general view that the deposition and mobilization of fat depends on the current supply of energy substrates which varies according to absorption but is presumably set against the background of energy consumption. So the rate of absorption less metabolic rate was chosen as the variable to which net lipogenesis or net lipolysis was proportional. I have tried using absorption rate alone, or absorption rate minus one constant for lipogenesis and another constant for lipolysis, but there may be less rather than more realism introduced into the predictions from such simulations, and the theoretical basis for such variables seems more arbitrary. It might be still more rational to determine lipogenesis or lipolysis by the net energy flow which also affects satiety/hunger, i.e. subtract current lipogenesis or add current lipolysis as well as subtracting metabolic rate from absorption rate to estimate pressure for lipogenesis or demand for lipolysis. After an adjustment of the proportionality factors, the results would be almost identical.

Lipolysis cannot be over about 10 cal/min in an energy flow model of hunger with symmetrical threshold values, or the prediction will be no eating by day or even no eating ever. The proportionality constant for lipolysis as absorption falls

below metabolic rate was therefore set at one-quarter, giving 7–8 cal/min at zero absorption. Much of the excess of absorption over consumption is presumably deposited in fat, that is, net lipogenesis involves a larger proportionality constant (Fig. 11). A simulation with the proportion set at three-quarters closely

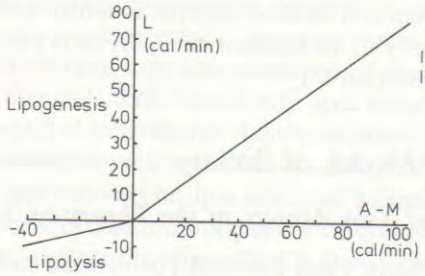

Fig. 11. Lipoflow functions in feeding model Mark 3, normal rat *ad libitum*. Lipogenesis is proportional to the excess of absorption over metabolic rate, taking three-quarters of the excess. Lipolysis is modelled to occur when absorption is less than metabolic rate, in proportion to the deficit, but not exceeding 10 cal/min even when absorption drops to zero, giving a deficit of 30–40 cal/min.

mimicked Le Magnen's lipogenesis estimates (Fig. 12). With a "basal" metabolic rate of 27 cal/min, to which 5 cal/min of activity expenditure is added in the dark, the generally accepted heat loss of 10% of the food energy produces a series of 2-h average metabolic rate predictions which also match Le Magnen's data tolerably well (Fig. 12).

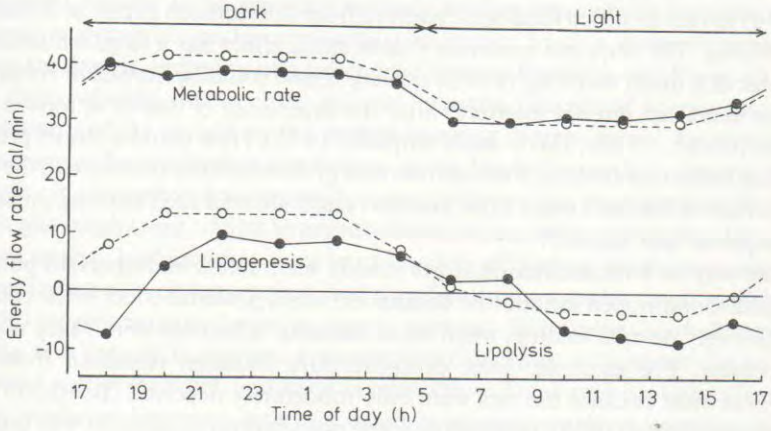

Fig. 12. Observed and simulated metabolic parameters in intact rats fed *ad libitum*, from Le Magnen and Devos (1970) and Mark 3 calculations.

These simulation results suggest that the circadian rhythm of lipogenesis and lipolysis is entirely secondary, and one does not have to seek a clock controlling the pancreas, although one may exist within the limits left by the parameter estimations for the modelling. The circadian rhythm of gastric clearance rate is a major determinant by its direct effect on absorption rate for a given amount in the stomach. The gastric rate function variation and the circadian motor activity rhythm also contribute indirectly to the lipogenesis–lipolysis rhythm, via their effects on the size of meals (Section V).

IV. Improved Model of Satiety

A. *Integration of Two Aspects of the Theory of Satiety*

The predictive success of the Mark 1 and 2 models Toates and I had developed was something of an embarrassment to my general theoretical stance on feeding control. While it was very encouraging to find the physiological hypothesis that energy flow determined feeding did work well in a physiological control model, I also believed that learning was very important in the control of feeding. Indeed, so had many other people for a long time, but in addition a considerable number of recent results had directly demonstrated major contributions to normal food intake both from the conditioning of aversions or preferences (Simson and Booth, 1973; Booth *et al.*, 1974) and from the conditioning of behaviour at the end of meals which was independent of the conditioning of choice or of rate of eating at the start of meals (Booth, 1972e; Booth and Davis, 1973). Evidence for this latter—acquired desatiating properties of arbitrary orosensory cues—had also been seen by Davis and Campbell (1973) and since by Kraly and Carty (1976) in rats in which food was removed from the stomach as fast as it entered by feeding. The acquired orosensory desatiating effect has a large influence on the size of a meal, doubling or even tripling it, and could be learned or relearned (when aversions did not interfere) after the experience of one or at most a few meals (Booth, 1972e; Davis and Campbell, 1973). How could a model predict feeding behaviour directly from current energy flow without reference to the oral properties of the food when experimental results showed such a strong influence of acquired oral control?

The way to a reconciliation is not readily seen unless an important point is noticed. Conditioned satiation or desatiation was a powerful effect in the context of relatively normal feeding, when other satiating influences were likely also to be present. For example, some postabsorptive satiation remained from the previous meal because the rats were only moderately deprived (Booth, 1972e; Booth and Davis, 1973), or possibly some postabsorptive satiation was created by the sham meal because a small fraction escaped the withdrawal procedures of Davis and Campbell (1973) or Kraly and Carty (1976). When the absence of

all other satiating influences is ensured by extended prior deprivation and efficient drainage of food from the stomach as it enters, there is at most a modest contribution from orosensory satiation which is extinguished by the very first sham feeding experience (Smith and Gibbs, 1976). One thing systems analysis teaches us is the foolishness of trying to understand the role of one mechanism in a system by running experiments designed to remove all other mechanisms: some, perhaps most, normally operative mechanisms must remain but their operation dissociated from the mechanism of interest by carefully designed and monitored manipulations. Specifically here, acquired oral satiation acts against the background of some degree of direct satiation. Indeed direct satiation effects may be presumed to work against a background of acquired orosensory satiation when they are imposed on free intake of a familiar diet (Booth, 1972a). An entirely successful demonstration of one category of effect is simply irrelevant to the question whether the other effect is also operative in that situation. Satiety may be assumed to be simultaneously learned and at least part postintestinal.

Now, by the end of 1974, the seriousness of an oversimplification in the gut component of Marks 1 and 2 was beginning to bear in on me. For all the speed with which absorption began, it was certainly not true that the current contents of the stomach were instantaneously affected by passage of food into the mouth and instantaneously reflected in the flow of energy into tissues. Even if oscillations arising from the delays in the duodenal–gastric control of gastric emptying were ignored, there was always present a delay between energy leaving the stomach and it entering the liver or the brain. The data on time of onset of rises in tissue radioactivity following the start of ingestion of radioactive starch showed that the lag for digestion, absorptive and circulation to tissue could be much less than 5 min in deprived rats (Pilcher *et al.*, 1974). However, such an experiment has yet to be reported in freely feeding rats, whose digestion and absorption dynamics might conceivably be slower; food in stomach certainly makes the gastric emptying of a saline load slower (Poulakos and Kent, 1973).

A delay of only two or three minutes between passage of energy into the duodenum and its arrival at the energy receptor system would have serious consequences for the feeding predictions in the Mark 2, exactly in the way that the delay in absorption has classically been the theoretical stumbling block over which glucostatic and similar hypotheses have tripped when pursued as far as to explain satiety. If absorption alone has to switch off feeding, meals seem certain to have to last a much longer time, and therefore (unless intake rate is somehow reduced) meals become larger in energy content. Within the Mark 2 model, feeding at a rate of 0·3 g/min, a simple delay of 3 min adds about 1 g to the predicted size of the meal, and so on in proportion. Total intake is little affected, as the predicted intermeal intervals lengthen approximately in compensation, but the point is that the real system has found a way of taking in that total in a fashion which yields smaller meals.

One possibility should now appear obvious: by summation or some other interaction, orosensory satiation on top of absorptive partial satiation provides the full intensity of satiety sufficient to stop feeding.

Nothing in a principle of simple summation requires that the orosensory satiation be acquired. However, such a system with experimentially independent oral satiety would have similar functional disadvantages to the substitution of a positive feedback, single-threshold system for a double-threshold system (discussed in Section II.B.1): meal sizes would be strongly subject to the vicissitudes of interaction between the temporal characteristics of the innate oral satiety system and variation in the timing of partial satiation due to variations in diet, feeding circumstances and so on. Sensory satiety, apparently some form of habituation, certainly exists in the rat for any familiar food stimulus, and the dysregulatory nature of such a mechanism is illustrated by the way that repeated dishabituation by change of food stimulus can cause marked overeating (reviewed in Booth, 1976).

Yet even if for such reasons one considers that useful control of meal size must depend on orosensory satiating influences acquired by experience of the effects of a food, there are still theoretical problems with simple addition of acquired and absorptive influences. By what behavioural process does a food stimulus suppress the intake of food? Conditioned satiety in the rat has usually been demonstrated with the food stimulus present from the start of the meal. Indeed it is hard to detect a satiating after-effect on removal of the stimulus (Booth and Davis, 1973, experiment 2; Holman, 1973). Does some sort of sensory inhibition accumulate as feeding proceeds? It is difficult to find any precedent for such a combination of habituation-like processes and associative control of performance. Furthermore, the oral stimulus which at the end of the meal is critical to inhibit (or, in the desatiation case, facilitate) feeding behaviour is the same stimulus that at the start of a meal is often facilitating (inhibiting in the converse case) food intake (experiments 2 and 3 of Booth, 1972e; experiments 1 and 2 of Booth and Davis, 1973). The behavioural effect could conceivably depend on the stage in the meal because of some timing process, but again this would not be well regulated, even if a plausible clock or counter could be found in the rat's behavioural organization. Alternatively, the direction of effect could depend on the internal stimuli which change as ingestion proceeds. That is, a stimulus which has conditioned attraction when the rat is hungry could have conditioned aversiveness when the rat is partly satiated (or vice versa on a conditioned desatiating diet). To put it another way, the mechanism is not *summation* of response tendencies to separate stumuli, but the generation of a response tendency by a *particular combination* of oral and postingestional stimuli which has been conditioned by the postingestional stimuli that eventually follow as digestion progresses.

A simple conception of such a combinatory mechanism would be that the

orosensory stimulus comes to select a particular (low) intensity of direct satiety as sufficient to stop feeding. The associative mechanism which establishes this selection would be some aspect of the postabsorptive consequences of the meal which contained that oral stimulus—the duration of satiety or its intensity. A formulation more precisely in terms of learning theory is discussed elsewhere (Booth, 1977; also Chapter 12, Section IV A).

B. *Feeding Model: Mark 3*

1. *Improvements on Mark 2*

Further to the changes I made in the calculation of lipogenesis and lipolysis (mentioned in Section III.C.3.) Mark 3 was created by adding three components to Mark 2: gut lag, conditioned satiety, and a feedback from fat store—all first programmed by Platt. We also altered the threshold variability routines.

(a) *Gut lag.* Toates and I had experienced the difficulties of even the crudest attempt to model the dynamics of digestion and intestinal absorption (Section II). At present the postulate of a simple delay between gastric clearance and energy flow detection may be realistic enough for many situations. With the conditioned satiety algorithm described next, the duration of the delay is not critical to the predictions by the model over a wide range of delay times. We commonly use what I believe to be a realistic value, say four minutes. The program empties the stomach according to the clearance function of Marks 1 and 2, but calculates the postabsorptive effects of a particular gastric emptying rate value with the prespecified delay after that rate occurred.

(b) *Conditioned satiety.* The rate of energy flow to the satiety/hunger receptor system which is sufficient to stop a particular meal is preselected at the start of the meal according to the record of the peak energy flow following the last meal with the same sensory characteristics. The "target" peak of energy flow remains 20 cal/min, the Mark 2 satiety threshold. If the last meal having the same sensory characteristics produced a peak energy flow over 20 cal/min, then the energy flow value at which feeding is stopped is lowered; if the last peak undershot target, the effective threshold is raised. For simplicity, the effective threshold is changed by the amount the target was misssed: the changes in energy flow rate following meals are sufficiently close to linear for such an equation generally to produce nearly all the conditioning or reconditioning of satiety after one meal, as the data indicate can indeed occur (experiment 2 extinction phase, Booth, 1972e). Lighting conditions are included among the sensory characteristics of a meal and so the effective satiety threshold settles to a value by day which differs from that by night because differences in clearance function and activity energy expenditure produce differing postprandial consequences of a given amount in

the stomach. Mark 3 has no provision for choice between diets, but the effects of changes in diets between or even within meals could be simulated: the sensory qualities of the diet would then also determine satiety threshold. They could also be programmed to determine feeding rate.

(c) *Threshold variability*. The detection of low and high threshold levels of energy flow, and the retrieval of the acquired satiety threshold value from memory, are all exact in simulations where only mean values of meal parameters and body parameters are required. In the real organism all these values will be subject to perceptual variability, and we introduced this as an option in the model. Platt and I represented this variability by adjustable normalized ranges of random numbers around the determinate threshold, but the stochastic properties of energy flow make such a routine yield a very skewed distribution of thresholds used. Mather and I have substituted random walks of the threshold value to be used. The effective threshold goes up or down on each calculation cycle by, say, one cal/min. At the hitherto determinate threshold value, the probability of a shift up or down is equal. At the limit set for the walk in any one direction, it becomes certain that the shift will be towards the central tendency. Between these extremes, probability varies linearly.

(d) *Feedback from stored fat*. Neither increments in lean body mass (growth) nor increments in adipose body mass, or its ratio to lean body mass (adiposity), are rigidly determined in the rat. Indeed it has been argued elsewhere that even the notion of some preset reference value determining body weight or fat store size is more misleading than helpful (Booth *et al.*, 1976; Booth, 1976; Garrow, 1975; Peck, 1976; Toates, 1975). This is not to deny that the degree of long term stability on body energy content is remarkable compared with the amount of energy that passes through the body. It is rather to point out that the organism has well known types of mechanism which could be used to maintain this stability and are considerably simpler in physical organization that the engineer's simplest set point machine, e.g. a thermostat. These are the mechanisms of compensating energy flows between compartments of the body.

If the present theory is right in identifying the hunger signal as net flow of non-lipid energy and the satiety signal as anticipated equivalent net gain of non-lipid energy, then the meal pattern should (if allowed to run freely) rather tightly control the long term gain in non-lipid energy according to the pre-existing structure of the body—sizes of stomach, muscles, brain etc. Indeed, there is evidence that lean mass turnover and feeding are tightly coupled (Pullar and Webster, 1974; Garrow, 1975). Fat mass is more easily displaced. However, there is evidence that large excursions of fat mass do have an inhibitory effect on feeding. The phenomena are clearer with increases in fat induced by overfeeding enforced by gastric intubations, electrical brain stimulation or insulin injec-

tions—when the forcing is removed from the fattened rat, it eats little or nothing until fat mass returns to within a modest fraction over the original, and food intake still remains low until body composition is in the normal range. In the case of ventromedial hypothalamic obesity, the size of the fat store is in equilibrium with food intake: forced excursions below the postsurgical stable value on a particular diet are corrected by overeating, and excursions above that stable value are corrected by undereating (Kennedy, 1953). A system would show these properties if the bias was more towards delivering energy to inhibit feeding the larger were the fat stores, and more to depositing energy the smaller the fat stores (Cohn and Joseph, 1962). The main energy flows into and out of fat are known biochemically, although quantitative details are unsettled. Clearly these flows are strongly affected by hormones. A simple feedback mechanism would involve some hormone-independent or "basal" characteristic. Basal lipolysis may in fact increase with size of fat cell (Smith, 1970; York, 1975). The resultant bias on glycerol supply to other tissues, or on the widely varying supply of non-esterified fatty acids, would in the long run produce a cumulated compensatory adjustment in food intake. The speed and robustness of the compensation would depend on characteristics of this component of energy flow *in vivo* which have yet to be measured. A systems analytic viewpoint makes it clear that signal persistence is the secret of long term control, not high precision or large magnitude.

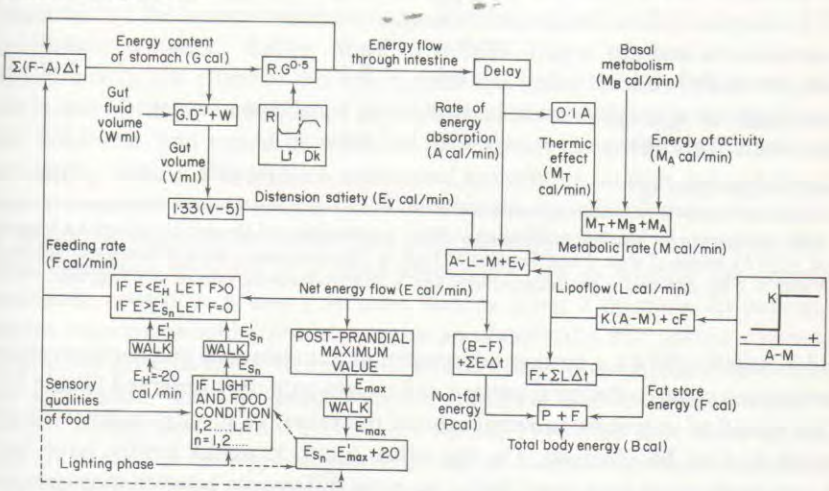

Fig. 13. Feeding model. Mark 3. The flow diagram defines the letter symbols used. "Walk" refers to the probabilized walk of hunger threshold, acquired satiety threshold and maximum energy flow recorded after a meal: these values shift around their mean values to represent the noise in the measurement of energy flow level by the hunger/satiety receptor system. Broken lines represent the retrieval of information from memory of the lighting conditions and sensory qualities of the food at the last feeding or of the acquired satiety value ($E_{S,n}$) which was established for the current lighting and foodstuff.

On these grounds, I wrote a fat feedback equation into Mark 3 which has no noticeable effect from one day to the next, as fat stores do not change that fast, but does ensure that an extra 30 or 50g of adipose tissue on a 300–400g rat almost completely inhibits feeding. The calculation simply adds one cal/min of lipolysis to the net energy flow to satiety for every 10g of fat gained.

With these additional components incorporated, the Mark 3 version of the feeding model reached in 1975 can be represented diagrammatically as Fig. 13.

2. *Predictions from Mark 3 Modelling*

(a) *Freely fed intact rats.* Le Magnen and Devos (1970) and colleagues (1973) are the only ones as yet to report metabolic estimates from respiratory dat in conjunction with meal pattern statistics in the freely fed rat. The Mark 3 predictions of the lipogenesis–lipolysis and metabolic rate cycles were given in Fig. 12. The feeding pattern predicted by the same simulation is given in Table V. A rather different pattern of meal sizes and intervals was reported by Becker

Table V
Characteristics of intact Wistar rats from Le Magnen's laboratory

	Reported characteristics				
	1968	1970	1973M	1973F	Simulated
Total intake in dark (g)	13·0	17·3	13·8	12·6	12·8
Meal size in dark (g)	2·6	3·1	—	—	3·2
Total intake in light (g)	8·5	5·1	4·4	3·5	4·2
Meal size in light (g)	2·0	1·6	—	—	2·1
Daily weight gain (g)	—	—	1·95	—	2·0

Data taken from Le Magnen and Tallon (1968), Le Magnen and Devos (1970) and Le Magnen *et al.* (1973), males of Exp. 1 and females of Exp. 3. The simulation has gut clearance factors of 0·8 and 1·1 by day and night respectively, and a basal metabolic rate of 27·5 cal/min.

and Kissileff (1974); a modest adjustment in gut clearance constants produces predictions close to the meal pattern and weight gain they observed (Table VI). This would of course be unremarkable if the values of most parameters in the model had to be changed. On the other hand, it could hardly have been objectionable to do that, considering the great differences between measurement and treatment conditions in the two laboratories. In particular the Americans used liquid food.

(b) *Rats with ventromedial hypothalamic lesions.* Mark 3 simulations of data from Becker and Kissileff (1974) are given in Table VI. The maintenance of lipogenesis during the day, and indeed the frequent meals, could only be

Table VI
Characteristics of female Wistar rats reported by Becker and Kissileff (1974)

	Pre-lesion ($n=15$)		1–3 days after WMH lesions ($n=7$)	
	Observed	Simulated	Observed	Simulated
Total intake in dark phase (g)	17·1	16·4	18·9	19·0
Average meal size in dark (g)	2·6	2·7	3·6	3·5
Total intake in light phase (g)	4·2	4·2	20·2	20·6
Average meal size in light (g)	2·1	2·1	3·8	4·2
Daily weight gain (p)	2·75	2·9	10·8	12

Simulations were based on a day gut factor of 0·8 changing to 1·25 after lesions and a night gut factor of 1·1 changing to 1·25. Basal metabolic rate was 27 cal/min throughout. The lipogenesis factor was raised from 0·75 to 0·85 after lesions.

simulated by including the assumption of a fast gastric clearance function in daylight. In fact, a somewhat faster clearance than normal by night as well seemed necessary to reach the total intake observed. However, changes in the gastric clearance function alone were not sufficient to produce realistic predictions of meal size by day (the conditioned satiety algorithm drove them very small by interaction with the gut lag). A good simulation was achieved by assuming that the lesion caused an increase in the proportionality constant of the lipogenesis equation, as in Mark 1 VMH lesion simulations (Section III.C.1.b.(ii)). The effect of this assumption was tested because hyperinsulinaemia is one of the best established physiological abnormalities in the ventromedial syndrome, and would be expected to augment lipogenesis. Of course the developing obesity also implies augmented lipogenesis (and/or reduced lipolysis). At present it is not possible to tell whether the hyperinsulinism is secondary to speeded absorption, and after some time adaptation of the pancreas to give a larger secretory response to a given absorption rate, or whether the changed pancreatic control is primary as some believe. Even if primary, an increased insulin response would still also require an abnormally fast gastric clearance constant to give the full VMH syndrome, according to variations I have run of this simulation, and the speeded gastric emptying and absorption would be mainly, though perhaps not exclusively (Gold, 1975), by day. More detailed data are needed on the physiological and feeding-pattern responses immediately after the VMH lesion. In particular, after surgery carried out with the stomach empty of food we need tests for hyperinsulinism or hyperinsulinaemic response to food cues before any food has been ingested.

(c) *Rats with lateral hypothalamic lesions.* The average feeding pattern of the classical recovered lateral rat may be a blurred composite of a complex and variable conjunction of abnormalities induced by such a diffuse lesion. The

slowed feeding rate of the Mark 1 lateral simulation (Section III.C.1.b.(iii)) was combined with a slowed stomach clearance constant to give the simulation of Table VII. An increase in basal metabolic rate and the circadian pattern of energy expenditure would also be worth simulating.

Table VII
Preliminary simulation of recovered lateral hypothalamic rat

Total intake in dark phase	9·4g
Average meal size in dark	4·6g
Total intake in light phase	2·3g
Average meal size in light	4·6g
Daily weight gain	0g

This simulation was based on a feeding rate lowered to 0·1g/min. and gut factors lowered to 0·6 at night and 0·4 by day. Metabolic rate was nor raised. not its circadian rhythm changed.

(d) *Rats on a deprivation schedule.* At least at some values of other parameters, simulations which include adaptive hyperlipogenesis show augmented meal sizes via the conditioned satiety mechanism. However, this effect does not seem nearly strong enough to produce 8-g meals. Probably the stomach clearance function also adapts to the deprivation schedule. Also the expectation of feeding after extended deprivation may produce such strong receptive relaxation of the stomach that neither postabsorptive satiety from pumped chyme not gastric or duodenal distension-induced distress are generated within the meal. even though when tone returns to the gastric musculature the stomach's large contents would cause very fast emptying and absorption and hence a very high rate of lipogenesis even without pancreatic or adipose adaptation. It remains to be seen whether some combination of such adaptations and learning mechanisms can account quantitatively for the large first meal following deprivation on a schedule. No other theory yet has.

(e) *Rats in the cold.* Since our first attempt to simulate the feeding of cooled rats with nothing more than a raised heat loss in a Mark 1 model (Section III.C.1.b.(vi)), Kraly and Blass (1976) have found evidence of increased gastric emptying within 1·5h of rats being placed in the cold. Less of a liquid meal was recovered via a fistula from the stomach when rats which had been deprived at room temperature were transferred to 5°C than when they remained at room temperature. The square root rate constant (calculated from the meal size and the last recovery measurement) increased by 45%. They also observed an increase in intake rate in the cold by about 40%.

The first meal on presentation of the milk diet is particularly difficult to simulate as the adaptations to the 24-h deprivation cycle remain unspecified (subsection (d), above). Hence, a Mark 3 simulation was started at the end of the first meal, taking as input the observed somewhat larger first meal in the cold. Both the reduced meal sizes and also the proportionately even further reduced intermeal intervals are predicted. Slow eating and fast gastric clearance cause the small meals, and fast gastric clearance reduces the intermeal interval for a given meal size. The increased metabolic rate in the cold, estimated from Wunder's (1975) equations, tends to increase meal size but to reduce intermeal interval still further.

The increased metabolic expenditure to maintain body temperature will also keep animals which have been deprived immediately previously under the same conditions at a lower net energy flow to the satiety/hunger system, assuming that lipolysis does not completely counteract this effect. This greater deficit in energy flow below hunger threshold would presumably be reflected in more vigorous appetitive behaviour. Thus, although the parameter values for a computer simulation would be fairly arbitrary, such an extension of the model would predict the increased operant rate in the cold observed by Kraly and Blass (1976).

Kraly and Blass (1976) adduce a peripheral sensation of cold as the motivating stimulus. These simulations suggest that heat loss could be the sufficient stimulus, and it could trigger the gastric change too. These two accounts are quite compatible, although it is not clear whether one should say the sensation mediates the effects of heat loss or vice versa—or should reject the implicitly over-linear view of causation involved in such verbal formulations.

(f) *Other states.* Short light–dark cycles have been found to entrain the rat's activity, vigilance and sleep rhythm to a large extent, although a residual free-running circadian variation can still be seen (Borbely and Huston, 1974; Borbely, 1975). The simulation of such conditions is critically dependent on the time course of changes in the gastric clearance rate factor from one lighting phase to the other. Progressively stronger entrainment of feeding to light change could indeed reflect an adaptation which produces more rapid changes in clearance rate constant.

Changes in the palatability or accessibility of the diet will be represented in the present model as constraints on feeding rate. Without close physiological specifications of the adaptation and learning consequent to initial exposure, it would not be wise to attempt to simulate the observed feeding patterns. Booth (1972f) showed that the responses to changes in palatability and access duration involved several distinct mechanisms, in interaction with the energy density of the diet. Hopefully, the results of all the above modelling will educate others as they have me into doubting that mere behavioural observation of the effects of

dietary manipulation is going to advance our understanding of the control mechanisms operative in intact rats or in experimental preparations of various sorts. Gastrointestinal, hormonal and systemic metablic processing must also be monitored while the rats are under maintenance conditions.

V. Conclusions

A. *There the Glove Lies*

This model of feeding is a steed fit for a good few more jousts yet. Give me the data on the rat's physiology and diet and I'll put the values into the model which will yield a prediction of the rat's feeding behaviour. Wrong predictions will interest me more than right ones—although a right prediction is more satisfying than a wrong one until the reason for the wrong prediction has been diagnosed!

The beast runs backwards too. If we have the details of a deviant feeding pattern, the model can be used to provide a qualitative or even quantitative analysis of possible causes—orosensory, gastrointestinal, hormonal-metabolic, satiety or hunger biases, associative operations.

The simulations just described impress one less with their accuracy than with their exposure of our ignorance of the relevant details of what is happening in the rat on a deprivation schedule or suffering from obesity, diabetes or any specific cerebral knife-cut, catecholamine depletion or whatever. Even if an experimenter is interested only in observing the conveniently large behavioural abnormalities resulting from unphysiological disruptions of the system, there is still no substitute for experimentally controlled physiological, biochemical and psychological analyses of the critical processes behind the behaviour. It is to be hoped that the model will draw attention to useful experimental designs.

A systems analysis that covers the phenomena of current and past interest is a *paradigm*—a structure within which to experiment, and unlikely to be refutable by any one single finding. Hopefully the present analysis is an approximation whose eventual dismissal will identify it as a special case or simplification, not as erroneous through and through. The particular Mark 3 model described in this chapter is of course only one family of simulations out of a potential tribe of mechanical embodiments of a theory of hunger, or of feeding in the rat in particular. If the variety of models becomes too great, it can be a serious problem to determine whether the models do have a family resemblance. At the moment, to my mind connection between the model and the theory is clear, but even that is not to claim that the model uniquely represents my theory. Indeed, I suspect that the model could be adjusted to be compatible with many of the physiological or psychological hypotheses put forward by other authors in this book. The question which can then be asked is whether one adjustment fits all the data on components and overall performance better than another adjustment.

B. *What have we Learnt?*

1. *Generalities*

One moral might be that we cannot afford to ignore the fine details in time or quantity of behavioural and physiological process. This, out of context is an almost useless aphorism, for the problem is choosing the significant detail our of the infinitie flux of collectable data. In context, however, there are specific pointers to what might be worth measuring in addition to daily food intakes and body weights.

Another abstract conclusion would be that simple principles which are already well established explain more than some of our more complicated theorizing seems to allow. Also the workability of the Mark 3 model has several general implications as to the status of the theorizing behind it.

(a) *Coherence.* I am sceptical of my ability to work our intuitively the implications of my physiological and learning process theory of hunger. I know from experience that I am too stupid to co-ordinate more than two or three definite hypotheses at once without sometimes committing logical fallacies. The attraction of mechanized synthesis of an explicitly analysed system is that it can release scientific understanding from the limited capacity of the individual human mind. There remains the need to keep a feel for the overall system, and to keep the management of model development tightly disciplined. Fast serial calculation can keep track of interactions too numerous to hold in mind at once, but it will mechanically follow up as many as you give it; so they must be kept to a minimum.

The computability of a model of a theoretical system establishes the absence of several incoherences that can afflict verbal or diagrammatic analysis.

(i) *Consistency.* Unnoticed self-contradiction can creep in, for example between the account of one phenomenon on one page and the account of another on the next. If the same computer program provides a simulation of both phenomena with only a change in input values, this sort of error does not exist.

(ii) *Explicitness.* As any programmer knows, it is all too easy to have a specification turn out to be ambiguous. Despite all the polemics in psychology about definition and operationalizability, hypotheses about feeding control are not often programmable without a lot more work to tie then down to useable procedures.

(iii) *Completeness.* The author and the reader can find a systematic verbal theory convincing, when in fact their intuition carries them over unnoticed gaps in the analysis. From the elemental loop onwards, our modelling was centred on the analysis of those consequences of feeding behaviour which seemed likely to have major effects on feeding behaviour. An experimentally or even metaphysically blinkered analysis of consequences or causes is hardly likely to be complete. On the other hand, a rough-and-ready outline analysis of likely major

processes or their correlates can prove robust enough for a working model to survive the fires of detailed refinement.

(b) *Adequacy.* The model does not merely succeed in crunching numbers *ad libitum* without dying. In additon, all the numbers are about right. More precisely, the simulations generally can produce output values within the range of values observed in reality, from functions and parameter values in the components which are again within the range of empirical plausibility. That is, the model shows that the theory behind it is adequate to the available data, at least for phenomena which have been simulated to date.

One can bandy words for hours, even years, on the relevance of particular processes or the power of a systematic set of hypotheses. Program a version of the systematic hypotheses and show mechanically what follows. Mere argument can then be briefer, or at least more cogently directed.

(c) *Verisimilitude.* Adequacy does not imply truth. There might be theories incompatible with mine for which models could be constructed which were also adequate to the data. Let us hope that there will soon be another example of a quantitatively predictive model of feeding patterns which relies on components with independently empirically measurable characteristics. It is hardly likely that a critical experiment will decide between the models or the theories, but one paradigm should prove more productive than the other, sooner or later. Compare the evidence for, and performance of, rival programmed feeding systems and you are almost bound to have learned something about hunger.

2. *Specifics*

The present theory and the Mark 3 version of the computable model of it have particular aspects which relate to other workers' theories. Metabolic control of feeding is a notion which has been in the field for a very long time, and indeed in the form of Mayer's glucose utilization theory of satiety/hunger has dominated the field for more than 20 years. The present theory is unusual in combining metabolic control and learning, each being essential to the successful operation of the other. Lip service has also long been paid to the role of learning in feeding, although not generally by those interested in metabolic factors—Le Magnen being the main exception. However, his work of the 1950s and early 1960s and the last decade of work on conditioned aversions does not extend experimentally to conditioning effects of normal foods *ad libitum,* a gap I have been attempting to fill since the late 1960s (Booth, 1969; 1977), inspired by Le Magnen (1956) and mildly aggravated by Rozin and Kalat (1971) and Garcia *et al.* (1974).

I was also encouraged to stop looking for hunger signals, and to lose any major interest in interfering with blood composition and tissue metabolism, by

Le Magnen and Tallon's (1966, 1968) analyses of feeding patterns in the rat, and instead to look for satiating effects of normal food, particularly postabsorptive effects. We found that we could identify postabsorptive satiation and that it developed as energy was delivered to the tissues relatively independent of the chemical nature of the energy-yielding substrate, and so I formulated the view that it was the nutrient utilization rates in critical tissues which cause satiety (Booth, 1969, 1971, 1972a,d; Booth and Jarman, 1976). It seemed a very obvious step for a biochemist to take, to invoke the Krebs tricarboxylic acid cycle to explain the similarities in satiating power of starch, protein and fats. A translation of Ugolev and Kassil (1961) I saw two years later showed that it was obvious enough to have been anticipated by at least nine years. I have only recently noticed that Kleiber's (1936) hydraulic model of energy flow through the organism includes a link to "regulation of appetite", which takes the basic idea far further back, although Kleiber seems never to have exploited it, and the homeostatic theorists of the 1950s ignored it.

(a) *Integration of fat in feeding control.* Le Magnen himself had gone on to measure metabolic correlates of feeding (Le Magnen and Devos, 1970; Le Magnen *et al.*, 1973) over the same period. Also around this time, Panksepp (1971) was studying the equivalence of different foodstuffs in their effects on food intake. Nicolaïdis was also considering the potential signalling power of the rate and acceleration components of absorption transients after a meal, and formulated his ischymetric theory (Nicolaïdis, 1974). The ideas of these three workers and myself on the metabolic control of feeding seem identical in many respects. Detectable differences arise when we suggest how fat might be integrated into the system. My idea is that fatty acids delivered physiologically are additive with other substrates according to their energy yield, to the tissues such as the liver. The model is written in this way and includes both phasic and basal components of lipolysis in the energy flow account. Le Magnen has invoked the Randle cycle, however, in support of a concept of modulation of glucose metabolism by free fatty acids. This modulation would not, I think, necessarily be proportional to energy, but could give free fatty acids an effect stronger than their energy yield. The model shows that, on the assumptions it incorporates, the lipolysis flow rates Le Magnen has observed can account for the correlated feeding pattern as he has suggested but purely by an additive effect of the modest energy supply rate from fat mobilization. Furthermore, a purely subtractive effect of lipogenesis has a substantial influence postprandially at the parts of the day when the stomach empties quickly. Postulates of long term regulatory mechanisms provide a major difference between both Panksepp and Nicolaïdis and myself. The same integration of energy flow appears sufficient from the model simulations, if energy flow from adipose fat stores is modulated slightly by the size of those stores. Panksepp (1972) and Nicolaïdis (1974), on

the other hand, posit a hypothalamic specialization which "witnesses to" or "parallels" to the peripheral adipose store by its own triglyceride content or fat metabolism (Panksepp and Pilcher, 1973; Nicolaïdis *et al.*, 1974). These postulates seem to me theoretically cumbersome, and experimentally it will be extremely difficult to demonstrate that a "fat head" actually mediates long term regulation, even if a cerebral correlate of normal variations in peripheral adiposity is in due course substantiated.

Hopefully the long term stability characteristics of Mark 3 simulations will dispel a number of misconceptions which appear to have confused some discussion on long term regulation in connection with control of feeding. The level or the direction of movement of fat mobilization, plasma non-esterified fatty acids, glycerol, or whatever, just before or just after meals is no basis for diagnosing "the role of free fatty acids in hunger". These transients may bear little relation to the instantaneous utilization of fatty acids by the relevant tissues, and the current utilization which is postulated to control feeding may in fact be averaged over a period of the order of the blood circulation time in the rat (about 1 min). Even the moment-to-moment relation between effective current utilization rate and propensity to feed may not reveal the most important role of fatty acids in feeding control. Current utilization could vary widely (no doubt usually compensated by co-ordinate variations in supply of other substrates) but the net effect averaged over a couple of meals or a day be nil. If however, in addition to influences tending to yield a null balance of free fatty acid supply, there is an influence tending to mobilize or deposit fat, the model predicts suppression or facilitation of feeding in consequence. If this bias is small, it will be difficult even to detect without very careful experimental design, let alone measure the mobilization bias or the food intake reduction. Yet the long term effect of the slightest bias will be for free fatty acids to reduce meal size, increase intermeal interval, or (generally) both, and to slim down the animal. Water flows over a waterfall with no perceptible effect on the rock, and a widely varying rates between dry and wet seasons; nonetheless, the retreat of the waterfall upstream over the decades is highly predictable while the bedrock is constant in composition. Even a simple dynamic equilibrium has an equilibrium point, partly set by "external" conditions, but well defended at its stable value without any mechanism for comparing the current value with an equilibrium value preset by some other mechanism. The mere interaction of the anatomically separated sets of chemical equilibria around the body provides even more strongly defended stabilities in the long term average values of many overall chacteristics of the system. Witness the stability or the mere three of four equilibria which constitute the Mark 3 model.

(b) *Parenteral receptors.* Russek's elegant model of feeding control (Russek, 1976; Chapter 10) is built round a hepatic glucoreceptor mechanism which he

has long argued is the main control of satiety and hunger. Oomura (1976) and colleagues have been accumulating evidence that hypothalamic neurones have at least two types of sensitivity to glucose as well as responding to insulin and fatty acids. It remains to be seen whether these are rivals to an energy flow theory or forerunners of a reduction of the overall theory by biochemical fractionation. Any specialized cellular receptor mechanism will still need the metabolic "frontage" which our modelling has presupposed (Booth and Toates, 1974b), recently reviewed by Friedman and Stricker (1976). Physiological and biochemical modelling are succinctly reviewed by Garfinkel *et al.* (1974). Although none of our modelling descends yet to the molecular, enzymic or cellular level, the key physiological parameter, energy substrate flux, is biochemically meaningful—indeed, currently being measured in our laboratory. The biochemical reduction will come when the relevant processes have been located and their normal operations measured.

(c) *Brain processing.* This model says a lot about guts and blood and tissues, and a little about mouth and nose and eyes. A lateral hypothalamic appetite centre and a ventromedial hypothalamic satiety centre have not been mentioned. This is because I do not believe they exist(Booth, 1976). However, it would be perverse to take the model to give no major role for the brain in feeding control. Feeding rate, however little or much an expression of nutrient-conditioned preference/aversion, is undeniably a product of sensorimotor control. Conditioning itself requires a change in cerebral properties serving to permit retrieval of past contingencies. The gastric and hormonal functions that can vary in the model probably do so largely under central control.

A neurophysiological reduction of the implied central processes would include, for example, the substitution of feeding rate by transfer functions across sensory receptors and brainstem motor, orosensory and sensorimotor relays concerned with gnawing, chewing and swallowing. Activation of the receptor system by low energy flow would be transformed into net facilitatory influences perhaps relying heavily on catecholaminergic neurones, while activation by high energy flow might facilitate serotoninergic systems having a net inhibitory behavioural effect on sensorimotor and appetitive systems.

The lesson from the realism of a model replete with peripheral processing is that we should not hasten unduly fast to invoke central processing mechanisms to explain characteristics of behaviour which can be explained by well known changes in non-neural processes without any change in the input–output characteristics of the neural feeding system. The simpler, or at least the more explicit, our specification of what the brain has to do, the more chance neuroscience has to begin solving the problem that certainly is there to be solved—how neuronal systems interrelate to organize behaviour within specified external and internal environments.

REFERENCES

Ackerman, E., Gatewood, L. C., Rosevear, J. W. and Molnar, G. D. (1965). Model studies of blood-glucose regulation *Bull. math. Biophys.* **27**, Special issue, 21–37.

Baile, C. A., McLaughlin, C. L., Zinn, W. and Mayer, J. (1971). Exercise, lactate, hormones and gold thioglucose lesions of the hypothalamus of diabetic mice. *Am. J. Physiol.* **221**, 150–155.

Balagura, S. and Devenport, L. D. (1970). Feeding patterns of normal and ventromedial hypothalamic lesioned male and female rats. *J. comp. physiol. Psychol.* **71**, 357–364.

Becker, E. E. and Kissileff, H. R. (1974). Inhibitory controls of feeding by the ventromedial hypothalamus. *Am. J. Physiol.* **226**, 383–396.

Booth, D. A. (1969). Metabolic factors affecting feeding and their regulatory role. Paper presented to British Association for Advancement of Science, Exeter, September 1969.

Booth, D. A. (1971). The control of feeding in metabolic regulation. Paper presented at IVth International Conference of the Regulation of Food and Water Intake, Cambridge, August 1971.

Booth, D. A. (1972a). Satiety and behavioural caloric compensation follow intragastric glucose loads in the rat. *J. comp. physiol Psychol.* **78**, 412–432.

Booth, D. A. (1972b). Feeding inhibition by glucose loads, compared between normal and diabetic rats. *Physiol. Behav.* **8**, 801–805.

Booth, D. A. (1972c). Some characteristics of feeding during streptozotocin-induced diabetes in the rat *J. comp. physiol. Psychol.* **80**, 238–249.

Booth, D. A. (1972d). Postabsorptively induced suppression of appetite and the energostatic control of feeding. *Physiol. Behav.* **9**, 199–202.

Booth, D. A. (1972e). Conditioned satiety in the rat. *J. comp. physiol. Psychol.* **81**, 457–471.

Booth, D. A. (1972f). Caloric compensation in rats with continuous or intermittent access to food. *Physiol. Behav.* **8**, 891–899.

Booth, D. A. (1973). Feeding and the regulation of body energy. Paper presented at the International Symposium "Hunger and the Regulation of Body Energy", Ermenonville, France, October, 1973.

Booth, D. A. (1974). Food intake compensation for increase or decrease in the protein content of the diet. *Behav. Biol.* **12**, 31–40.

Booth, D. A. (1976). Approaches to feeding control. *In* "Appetite and Food Intake" (T. Silverstone, ed.). Dahlem Konferenzen, Berlin.

Booth, D. A. (1977). Satiety and appetite are conditioned reactions. *Psychosom. Med.*, **39**, 76–81.

Booth, D. A. (1978). Metabolism and the control of feeding in man and animals. *In* "Chemical Influences on Behaviour" (K. Brown and S. J. Cooper, eds). Academic Press, London and New York.

Booth, D. A. and Brookover, T. (1968). Hunger elicited in the rat by a single injection of crystalline bovine insulin. *Physiol. Behav.* **3**, 439–446.

Booth, D. A. and Campbell, C. S. (1975). Relation of fatty acids to feeding behaviour: effects of palmitic acid infusions, lighting variation and pent-4-enoate, insulin or propranolol injection. *Physiol. Behav.* **15**, 523–535.

Booth, D. A. and Davis, J. D. (1973). Gastrointestinal factors in the acquisition of oral sensory control of satiation. *Physiol. Behav.* **11**, 23–29.

Booth, D. A. and Jarman, S. P. (1975). Ontogeny and insulin-dependence of the satiation which follows carbohydrate absorption in the rat. *Behav. Biol.* **15**, 159–172.

Booth, D. A. and Jarman, S. P. (1976). Inhibition of food intake in the rat following complete absorption of glucose delivered into the stomach, intestine or liver. *J. Physiol., Lond.* **259**, 501–522.

Booth, D. A. and Pain, J. F. (1970). Effects of a single insulin injection on approaches to food and on the temporal pattern of feeding. *Psychon. Sci.* **21**, 17–19.

Booth, D. A. and Simson, P. C. (1974). The rejection of a diet which has been associated with a single administration of a histidine-free amino acid mixture. *Br. J. Nutr.* **31**, 285–296.

Booth, D. A. and Toates, F. M. (1974a) A computer model of hunger. Paper presented to the Experimental Psychology Society, Bristol, April, 1974.

Booth, D. A. and Toates, F. M. (1974b). A physiological control theory of food intake in the rat: Mark 1. *Bull. Psychon. Soc.* **3**, 442–444.

Booth, D. A. and Toates, F. M. (1974c). Control of food intake by energy supply. Paper presented at Vth International Conference on Physiology of Food and Fluid Intake, Jerusalem, October 1974.

Booth, D. A., Stoloff, R. and Nicholls, J. (1974). Dietary flavor acceptance in infant rats established by association with effects of nutrient composition. *Physiol Psychol.* **2**, 313–319.

Booth, D. A., Toates, F. M. and Platt, S. V. (1976). Control system for hunger and its implications in animals and man. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka and G. A. Bray, eds), pp. 127–143. Raven Press, New York.

Borbely, A. A. (1975). Circadian rhythm of vigilance in rats: Modulation by short light–dark cycles. *Neurosci. Letters* **1**, 67–71.

Borbely, A. A. and Huston, J. P. (1974). Effects of two-hour light–dark cycles on feeding, drinking and motor activity of the rat. *Physol. Behav.* **13**, 795–802.

Campbell, C. S. and Davis, J. D. (1974a). Licking rate of rats is reduced by intraduodenal and intraportal glucose infusion. *Physiol. Behav.* **12**, 357–365.

Campbell, C. S. and Davis, J. D. (1974b). Peripheral control of food intake: interaction between test diet and postingestive chemoreception. *Physiol. Behav.* **12**, 377–384.

Cohn, C. and Joseph, D. (1960). Effects on metabolism by the rate of ingestion of the diet, 'Meal eating' versus 'nibbling'. *Am. J. clin. Nutr.* **8**, 682–689.

Cohn, C. and Joseph, D. (1962). Influence of body weight and body fat on appetite of "normal" lean and obese rats. *Yale J. Biol. Med.* **34**, 598–607.

Davis, J. D. and Booth, D. A. (1974). Vagotomy in the rat reduces meal sizes of diets containing fat. *Physiol. Behav.* **12**, 685–688.

Davis, J. D. and Campbell, C. S. (1973). Peripheral control of meal size in the rat: effect of sham feeding on meal size and drinking rate. *J. comp. physiol. Psychol.* **83**, 379–688.

De Castro, J. M. and Balagura, S. (1975). Meal patterning in the streptozotocin-diabetic rat. *Physiol. Behav.* **15**, 259–263.

Friedman, M. I. and Stricker, E. M. (1976). The physiological psychology of hunger: a physiological perspective. *Psycho. Rev.*, **83**, 409–431.

Garcia, J., Hankins, W. G. and Rusiniak, K. (1974). Behavioral regulation of the milieu interne in man and rat. *Science, N.Y.* **185**, 824–831.

Garfinkel, D., Achs, M. J. and Dzubow, L. (1974) Simulation of biological systems at the level of biochemistry and physiology. *Fed. Proc.* **33**, 176–182.

Garrow, J. S. (1975). Regulation of body weight. *In* "Obesity: Its Pathogenesis and Management" (T. Silverstone, ed.), pp. 3–27. Medical and Technical Publishing, London.

Geertsema, S. P. (1973). Ontwikkeling analyse en toepassingen van enige modellen der regulatie van voedselopnamel. Ph.D. Thesis, University of Gronigen.

Geertsema, S.P. and Reddingius, H. (1974). Preliminary considerations in the simulation of behaviour. *In* "Motivational Control Systems Analysis" (D. J. McFarland, ed.), pp. 355–405. Academic Press, London and New York.

Gold, R. M. (1975). Hypothalamic hyperphagia despite imposed diurnal or nocturnal feeding and drinking rhythms. *Physiol. Behav.* **14**, 861–866.

Harris, L. J., Clay, J., Hargreaves, F. J. and Ward, A. (1933). Appetite and choice of diet. The ability of the vitamin B deficient rat to discriminate between diets containing and lacking the vitamin. *Proc. Roy. Soc. Lond.* **113**, 161–190.

Hirsch, J. (1972). Discussion. *Adv. psychosom. Med.* **7**, 229–242.

Hunt, J. N. and Knox, M. T. (1968). Regulation of gastric emptying. *In* "Handbook, of Physiology: Alimentary Canal, Vol. 4: Motility" (C. F. Code and W. Heidel, eds), pp. 1917–1935. American Physiological Society, Washington, DC.

Hunt, J. N. and Stubbs, D. F. (1975). The volume and content of meals as determinants of gastric emptying. *J. Physiol., Lond.* **245**, 209–225.

Kakolewski, J. W., Deaux, E., Christensen, J. and Chase, B. (1971). Diurnal patterns in water and food intake and body weight changes in rats with hypothalamic lesions. *Am. J. Physiol.* **221**, 711–718.

Kennedy, G. C. (1953). The role of depot fat in the hypothalamic control of food intake in the rat. *Proc. Roy. Soc., Lond., B* **140**, 578–592.

Kissileff, H. R. (1970). Free feeding in normal and recovered lateral rats monitored by a pellet-detecting eatometer. *Physiol. Behav.* **3**, 163–173.

Kleiber, M. (1936). Problems involved in breeding for efficiency of food utilization. *Proc. Am. Soc. Anim. Prod.* 247–258.

Kraly, F. S. and Blass, E. M. (1976). Increased feeding in rats in a low ambient temperature. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka and G. A. Bray, eds), pp. 77–87. Raven Press, New York.

Kraly, F. S. and Carty, W. J. (1976). Pregastric stimuli are sufficient for short-term satiety in 3-h deprived rats. Paper presented at Eastern Psychological Association meetings, New York.

Le Magnen, J. (1956). Effets sur la prise alimentaire du Rat blanc des administrations post prandiales d'insuline et le mécanisme des appétits caloriques. *J. Physiol., Paris* **48**, 789–802.

Le Magnen, J. (1971). Advances in studies on the physiological control and regulation of food intake. *In* "Progress in Physiological Psychology" (J. Sprague and E. Stellar, eds), Vol. 4, pp. 204–261. Academic Press, New York and London.

Le Magnen, J. and Devos, M. (1970). Metabolic correlates of the meal onset in the free food intake of rats. *Physiol. Behav.* **5**, 805–814.

Le Magnen, J. and Tallon, S. (1966). Le périodicité spontanée de la prise d'aliments ad libitum du rat blanc. *J. Physiol., Paris* **58**, 323–349.

Le Magnen, J. and Tallon, S. (1968). L'effect du jeûne préable sur les caracteristiques temporelles de la prise d'aliments chez le rat. *J. Physiol., Paris* **60**, 143–154.

Le Magnen, J., Devos, M., Gaudillière, J.-P., Louis-Sylvestre, J. and Tallon, S. (1973). Role of a lipostatic mechanism in regulation by feeding of energy balance in rats. *J. comp. physiol. Psychol.* **84**, 1–23.

Levitsky, D. A. (1970). Feeding patterns of rats in response to fasts and changes in environmental conditions. *Physiol. Behav.* **5**, 291–300.

Lovett, D. and Booth, D. A. (1970). Four effects of exogenous insulin on food intake. *Q. J. exp. Psychol.* **22**, 406–419.

McFarland, D. J. (1971). "Feedback Mechanisms in Animal Behaviour". Academic Press, London and New York.

Nicolaïdis, S. (1974). Short-term and long term regulation of energy balance. Paper presented at XXVI International Congress of Physiological Sciences, New Delhi, October 1974.

Nicolaïdis, S., Petit, M. and Polonowski, J. (1974). Etude du rapport entre la régulation de la masse adipense corporelle et la composition lipidique de ses "centres régulateurs". *C. hebd. Séanc. Acad. Sci., Paris* **278**, 1393–1396.

Norton, S., Culver, B. and Mullenix, P. (1975). Development of nocturnal behavior in albino rats. *Behav. Biol.* **15**, 317–331.

Oatley, K. (1967). A control model of the physiological basis of thirst. *Med. biol. Engng.* **5**, 225–237.

Oatley, K. (1971). Dissociation of circadian drinking pattern from eating. *Nature, Lond.* **229**, 494–496.

Oatley, K. (1973). Simulation and the theory of thirst. *In* "The Neuropsychology of Thirst" (A. N. Epstein, H. R. Kissileff and E. Stellar, eds), pp. 199–223. Winson, New York.

Oatley, K. (1974). Circadian rhythms and representations of the environment in motivational systems. *In* "Motivational Control Systems Analysis" (D. J. McFarland, ed.), pp. 427–459. Academic Press, London and New York.

Oatley, K. and Toates, F. M. (1969). The passage of food through the gut of rats and its uptake of fluid. *Psychon. Sci.* **16**, 225–226.

Oomura, Y. (1976). Significance of glucose, insulin, and free fatty acid on the hypothalamic feeding and satiety neurons. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka and G. A. Bray, eds), pp. 145–157. Raven Press, New York.

Paintal, A. S. (1954). A study of gastric stretch receptors. Their role in the peripheral mechanism of satiation of hunger and thirst. *J. Physiol., Lond.* **126**, 255–270.

Panksepp, J. (1971). Effects of fats, proteins, and carbohydrates on food intake in rats. *Psychon. Monog. Suppl.* **4**, 85–95.

Panksepp, J. (1972). Hypothalamic radioactivity after intragastric glucose-^{14}C in rats. *Am. J. Physiol.* **223**, 396–401.

Panksepp, J. (1973). Reanalysis of feeding patterns in the rat. *J. comp. physiol. Psychol.* **82**, 78–94.

Panksepp, J. and Pilcher, C. W. T. (1973). Evidence for an adipokinetic mechanism in the ventromedial hypothalamus. *Experientia* **29**, 793.

Peck, J. W. (1976). Situational determinants of the body weights defended by normal rats and rats with hypothalamic lesions. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka and G. A. Bray, eds), pp. 297–311. Raven Press, New York.

Pilcher, C. W. T., Jarman, S. P. and Booth, D. A. (1974). The route of glucose to the brain from food in the mouth of the rat. *J. comp. physiol. Psychol.* **87**, 56–61.

Poulakos, L. and Kent, T. H. (1973). Gastric emptying and small intestinal propulsion in fed and fasted rats. *Gastroenterology* **64**, 962–967.

Pullar, J. and Webster, A. J. F. (1974). Heat loss and energy retention during growth in congenitally obese and lean rats. *Br. J. Nutr.* **31**, 377–392.

Ralph, T. L. and Sawchenko, P. E. (1975). Hypothalamic lesions modify gastrointestinal transit in the rat. Paper presented at Eastern Psychological Association meetings, New York.

Rozin, P. and Kalat, J. W. (1971). Specific hungers and poison avoidance as adaptive specializations of learning. *Psychol. Rev.* **78**, 459–486.

Rupe, B. D. and Mayer, J. (1967). Endogenous glucose release stimulated by oral sucrose administration in rats. *Experientia* **23**, 1009–1010.

Russek, M. (1971). Hepatic receptors and the neurophysiological mechanisms controlling feeding behavior. *In* "Neurosciences Research" (S. Ehrenpreis and O. C. Solnitzky, eds), Vol. 4, pp. 213–282. Academic Press, New York and London.

Russek, M. (1976). A conceptual equation of intake control. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka and G. A. Bray, eds), pp. 327–347. Raven Press, New York.

Simson, P. C. and Booth, D. A. (1973). Olfactory conditioning by association with histidine-free or balanced amino acid loads. *Q. J. exp. Psychol.* **25**, 354–359.

Smith, G. P. and Gibbs, J. (1976). What the gut tells the brain about feeding behaviour. *In* "Appetite and Food Intake" (T. Silverstone, ed.). Dahlem Konferenzen, Berlin.

Smith, U. (1970). Effects of glucose and insulin on lipolysis rates in human fat cells of different sizes. *FEBS Letters* **11**, 8–10.

Steffens, A. B. (1969a), The influence of insulin injections and infusions on eating and blood glucose level in the rat. *Physiol. Behav.* **4**, 823–828.

Steffens, A. B. (1969b). Rapid absorption of glucose in the intestinal tract of the rat after ingestion of a meal. *Physiol. Behav.* **4**, 829–832.

Toates, F. M. (1974). Computer simulation and the homeostatic control of behaviour. *In* "Motivational Control Systems Analysis" (D. J. McFarland, ed.), pp. 407–426. Academic Press, London and New York.

Toates, F. M. (1975). "Control Theory in Biology and Experimental Psychology". Hutchinson Educational, London.

Toates, F. M. and Booth, D. A. (1974). Control of food intake by energy supply. *Nature, Lond.* **251**, 710–711.

Toates, F. M. and Oatley, K. (1969). Computer simulation of thirst and water balance. *Med. biol. Engng.* **8**, 71–87.

Ugolev. A. M. and Kassil, V. G. (1961). Fiziologiia appetita. *Uspekhi Sov. biol.* **51**, 352–368. [Translation 9-23-63, Library Branch, Division of Research Services, N.I.H.].

Wiepkema, P. R. (1971). Positive feedbacks at work during feeding. *Behaviour* **39**, 266–273.

Wiepkema, P. R., Prins, A. J. A. and Steffens, A. B. (1972). Gastrointestinal food transport in relation to meal occurrence in rats. *Physiol. Behav.* **9**, 759–763.

Wunder, B. A. (1975). A model for estimating metabolic rate of active or resting animals. *J. theor. Biol.* **49**, 345–354.

York, D. A. (1975). Lipid metabolism in genetic models of obesity. *Proc. Nutr. Soc.* **34**, 249–255.